EXHIBIT B

EXHIBIT A

to Ethicon's Response in Opposition to Plaintiffs' Motion to Exclude Dr. Larry T. Sirls' TVT/TVT-O General Opinions

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: ***Wave 2 Cases***	

Expert Report of Larry T. Sirls, MD, FACS

Credentials

I graduated Summa Cum Laude from the University of Detroit, 1983. I completed medical school at the University of Michigan 1987, then completed urology residency at Henry Ford Hospital in1992 and then fellowship training in Female Urology, Neurourology and Urodynamics at Kaiser Permanente Medical Center, Los Angeles in 1993. I returned as academic teaching faculty at Henry Ford Hospital 1993 – 1996, and moved to William Beaumont Hospital from 1996 to present.

I was introduced to urinary incontinence and pelvic prolapse in medical school with Dr. Edward McGuire, prompting my interest in urology. During residency, Aaron Kirkemo, a Shlomo Raz trained urologist joined our staff and brought current thought processes in pelvic prolapse, urinary incontinence and reconstructive urology. During urology residency, I had extensive experience in native tissue repair of urinary incontinence, fascial pubovaginal sling, vaginal approach needle suspensions and the Burch bladder neck suspension. This prompted my interest and ultimate selection of fellowship training in Female Urology focusing on reconstructive urology with Drs. Gary Leach and Philippe Zimmern in Los Angeles.

During residency and fellowship we did native tissue primary repairs of the bladder, apex, vaginal vault suspension and rectocele repair. We did not use any mesh material. Slings were traditional harvested fascial pubovaginal slings. We published on fascial sling procedure outcomes.

As a young staff physician, I did research on patient reported outcomes after bladder suspension surgery, an alternative device for urinary incontinence (Femsoft Insert), and bulking agents (Durasphere), in addition to bladder outlet obstruction related topics. I have been the primary investigator at William

Beaumont Hospital for the Urinary Incontinence Treatment Network since 2007 and have participated in several NIH trials on urinary incontinence evaluation and surgical treatment. I participated in the NIH funded stress incontinence surgery trial comparing fascial pubovaginal sling and Burch bladder suspension (SISTEr), the trial comparing retropubic and transobturator sling (TOMUS) and the trial evaluating the need for preoperative urodynamics in women having surgery for SUI (VALUE), including many secondary analysis looking at outcomes, quality of life, and complications. I have presented and published on the preoperative selection and evaluation, urodynamic testing before and after surgery, intraoperative experience and complications, and post-operative outcomes after surgery for SUI.

I am a Professor at the Oakland University William Beaumont School of Medicine and the Director of the Female Pelvic Medicine and Reconstructive Surgery fellowship program, one of the few Urology directed programs in the US. For more information on my qualifications, training, experience and publications, see my CV.

Synopsis

It is my opinion that the mesh midurethral sling (MUS) procedures such as the TVT and TVT-O represent the most significant advances in the surgical management of female SUI that I have ever observed. My opinion is based on 25 years of clinical experience; 12 years of performing fascial pubovaginal slings and Burch suspensions, followed by 13 years of placing both retropubic and transobturator mesh MUS. This opinion is formed from surgical experience and outcomes with thousands of women, reading and reviewing the literature, participating in scientific research and attending scientific meetings. I hold all of my opinions to a reasonable degree of scientific and medical certainty, and I reserve the right to update my opinions based on new information or materials provided to me. I am confident that polypropylene material is safe and effective

as a surgical implant.

I prefer the transobturator sling for several reasons, some of them outlined in the invited Journal of Urology opinion piece published in 2014 (Sirls, J Urol, 2014). Like many urologists, originally I preferred the TO outside in approach. Over time, and for very specific reasons, I changed to the TO inside out approach (TVT-O, Abbrevo) that I still use. I will use the RP MUS sling in specific situations, and have used both top down RP sling (SPARC) and the bottom up RP sling (TVT, TVT Exact).

Many randomized, controlled trials comparing types of MUS procedures, as well as comparing the MUS to other established non-mesh SUI procedures, have consistently demonstrated efficacy. MUS have been extensively studied in long-term follow-up after implantation and have demonstrated superior safety and efficacy. MUS procedures have been subject to more extensive investigation than any other surgical treatment for SUI. The FDA has clearly stated that the polypropylene MUS is safe and effective in the treatment of SUI. I believe that polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for my friends, family and patients, and this is supported numerous relevant professional organizations as later discussed.

Scope of the problem:

Stress Urinary incontinence is the loss of urine caused by increased physical activity such as coughing, sneezing or exercise. Studies estimate 30-50 % of women will have SUI (Nygaard I, et al., Obstet Gynecol 75:848-51, 1990, Nygaard I, et al., Obstet Gynecol 84: 183-87, 994, Vandoninck V, et al., BJU Int 94: 1291-95, 2004, Adelmann PK J Health Care Poor Underserved 15:99-112, 2004.). Women who exercise more have more SUI, particularly runners, and many women limit their physical activity because of this.

As our population ages, the prevalence of SUI increases. The rate of SUI peaks between 45-49 years of age and then begins to slowly decline, possibly secondary to decreased activity levels. Previous studies report that older women are more likely to have mixed stress and urgency incontinence (Diokno et al, 1986; Molander et al, 1990; Roberts et al, 1998; Nuotio et al, 2003), whereas young and middle-aged women generally report stress incontinence (Hording et al, 1986; Holst and Wilson, 1988; Burgio et al, 1991; Samuelsson et al, 1997; Hannestad et al, 2000).

Several studies show an association between vaginal deliveries and SUI (Elving LB et al., Scnad J Urol Nephrol Cuppl 125:37-43 1989, Burgio KL et al., Int Urogynecol J Pelvic Floor Dysfunct 7:69-71, 1996) by directly injuring the pelvic muscles and connective tissue that are necessary for pelvic support. This is not observed after C-section delivery.

Urinary incontinence can affect a woman's physical, psychosocial, and economic well being. They can experience psychological distress, social isolation and loneliness, increased falls and fractures and increased health care use (Bogner HR J Am Geriatr Soc 52: 1870-74, 2004). At least 75% of women are bothered by their symptoms, with nearly 1/3 moderately or extremely bothered. SUI specifically negatively impacts young and middle-aged women's quality of life, work performance and sexual activity (Margalith I, et al., Qual Life Res 13: 1381-90, 2004.)

The proportion of women with any UI in the past 12 months who report having sought medical treatment ranges from 12% (Sampselle et al, 2002) to 53% (Mardon et al, 2006) with about half the studies showing 25% to 30% (Rekers et al, 1992; Hannestad et al, 2002; Hagglund et al, 2003; Hsieh et al, 2008). All studies that have examined treatment seeking by type of incontinence have found that women with urgency or mixed incontinence are more likely to seek treatment than women with stress incontinence (Hannestad et al, 2002; Danforth

et al, 2006; Zhu et al, 2008). As expected, the proportion of women seeking treatment is strongly associated with frequency, severity, and symptom bother, with several studies reporting proportions of 50% to 80% of women with daily, moderate to severe, or bothersome incontinence (Hannestad et al, 2002; Kinchen et al, 2003; Diokno et al, 2004; Gasquet et al, 2006).

Prevalence of Urinary Incontinence in the Postpartum Female

Nearly all postpartum UI is stress related. Overall, it appears that any incontinence is reported by 15% to 30% of women during the postpartum year, weekly or greater incontinence is reported by 5% to 10%, and daily UI is reported by less than 5% of women. Excluding women with UI before pregnancy reduced the prevalence of postpartum incontinence by 3% to 4% in the one study reporting separate prevalences for each group (Glazener et al, 2006). Studies that included women delivered by caesarean section and delivered vaginally consistently found a lower prevalence in those delivered by caesarean section. Studies reporting prevalence in women delivered by elective caesarean section and by caesarean section after initiation of labor showed a substantially lower prevalence of postpartum UI in the elective caesarean section group.

Treatment Options for SUI

Strategies to treat SUI include behavioral modification, physical therapy, pharmacologic agents, devices including incontinence pessary and urethral insert, and investigational modalities including muscle derived cell injections.

Behavioral modification includes timed voiding, fluid restriction and avoidance of activities that may result in SUI, i.e., stop exercising, etc. For pure SUI, behavioral modification is usually incorporated into a wider program including pelvic floor PT. However, Fantyl and associates (Fantyl JA, Wyman JF, McLish DK, et al. Efficacy of bladder training in older women with urinary incontinence. JAMA 1991;265:609–13) demonstrated more than 50% improvement in leakage episodes and volume of urine lost with their program, getting essentially equal

results in patients with both SUI and UUI. This is enough improvement to satisfy many patients.

Physical therapy (PT) (NEJM) means the patient is being specifically trained in pelvic-floor muscle exercises and is generally regarded as first-line management for the condition. However, PT is associated with broad variation in the rates of subjective success (53 to 97%) and objective success (5 to 49%), and more severe symptoms are associated with worse outcomes. (Imamura M, Abrams P, Bain C, et al. Systematic review and economic modeling of the effectiveness and cost effectiveness of non-surgical treatments for women with stress urinary incontinence. Health Technol Assess 2010;14:1-188, iii-iv., Cammu H, Van Nylen M, Blockeel C, Kaufman L, Amy J-J. Who will benefit from pelvic floor muscle training for stress urinary incontinence? Am J Obstet Gynecol 2004;191:1152-7.) After 3 to 15 years, 25 to 50% of women initially treated with PT have proceeded to surgery. (Lamers BHC, van der Vaart CH. Medium- term efficacy of pelvic floor muscle training for female urinary incontinence in daily practice. Int Urogynecol J Pelvic Floor Dysfunct 2007;18:301-7., B. K, Kvarstein B, Nygaard I. Lower urinary tract symptoms and pelvic floor muscle exercise adherence after 15 years. Obstet Gynecol 2005;105:999-1005.)

An important study was recently published in NEJM by a multicenter Dutch group (24% of all Dutch hospitals participated). They randomly assigned 230 women to surgery and 230 women to PT. A total of 49.0% of women in the PT group and 11.2% of women in the surgery group crossed over to the alternative treatment. Subjective improvement was reported by 90.8% of women in the surgery group and 64.4% of women in the PT group (intention to treat analysis). Subjective cure was reported by 85.2% in the surgery group and 53.4% in the PT group. The rates of objective cure were 76.5% in the surgery group and 58.8% in the PT group. A post hoc per-protocol analysis showed that women who crossed over to the surgery group had outcomes similar to those of women initially assigned to surgery and that both these groups had outcomes superior to those of women

who did not cross over to surgery. This is important Level 1 evidence that in women with stress urinary incontinence, initial midurethral-sling surgery with TVT and TVT-O, as compared with initial PT, results in higher rates of subjective improvement and subjective and objective cure at 1 year.

Devices

Pessaries are vaginal devices commonly used to reduce pelvic organ prolapse. Pessaries have been used for SUI also. Pessaries are potentially applicable to the majority of the incontinent population (those with pure stress or mixed UI and urethral hypermobility), do not require specific testing, such as urodynamics and can be used “as needed” for predictable SUI (as can the other devices). However, pessaries have side effects including vaginitis and local discomfort, vaginal spotting from erosion and often the need for the pessary to be removed with sexual activity. Pessaries do not correct intrinsic sphincter deficiency and do not definitively treat potentially curable problems.

Urethral inserts for SUI passively occlude and/or coapt the urethra and must be removed for voiding. Although urethral inserts are potentially applicable to almost all women with pure SUI and possibly some of those with mixed UI, it must be remembered that the device must be removed and replaced for each void. Despite the new soft, hydrophilic materials, only a small percentage of the SUI population seems to be willing to instrument the urethra to be dry. The highest patient acceptance seems to be among those with very predictable, episodic SUI, such as during sports like running or golf, or dancing.

Anatomic basis of SUI

Females are much more likely to suffer from UI due to sphincteric deficiency than males because of the much less powerful sphincteric mechanisms. The female bladder neck is a far weaker structure than the male bladder neck and is often incompetent, even in nulliparous young women (Chapple et al, 1989).

Urinary continence usually relies on the integrity of the urethral sphincteric mechanism in females. The female urethra is composed of a longitudinal intrinsic urethral smooth muscle and a larger extrinsic striated muscle component. This sphincter extends throughout the proximal two thirds of the urethra, being most developed in the middle one third of the urethra. Therefore in women the majority of the urethra should be considered to be sphincter active. Damage to the innervation of the urethral sphincter (in particular the pudendal nerve) by obstetric trauma reduces the effectiveness of this mechanism and predisposes to stress UI.

Normal female sphincteric function depends on integration of a number of factors:

1. Watertight closure of the urethral mucosa, or the “mucosal seal effect”. The urethra is not simply a closed tube but there are mucosal folds with potential spaces for urine leakage. In women estrogen and a cushion effect of the submucosal vasculature are felt to contribute to the mucosal seal (Raz et al, 1972; Tulloch, 1974).
2. Compression of the urethral wall. External compression of the urethra includes smooth and striated muscle tone, mechanical factors related to transmission of abdominal pressure, and structural (anatomic) support of the posterior urethral wall.
3. Structural support to keep the proximal urethra from moving during increases in pressure.
4. Intact neurologic function.

Conditions Causing Sphincter Abnormalities

The causes of sphincteric dysfunction are different in men and women. In men, sphincter abnormalities are most commonly caused by prostate surgery, trauma or neurologic disease.

Labor and delivery have long been thought to be risk factors for stress incontinence, urogenital prolapse, and anal incontinence. Vaginal delivery may be associated with direct injury to the pelvic soft tissues, as well as partial denervation of the pelvic floor and is felt to play a strong role in the etiology of stress urinary incontinence (SUI). Others have shown that multiparity, forceps delivery, increased duration of the second stage of labor, (maybe related to epidural anesthesia), third degree perineal tear; and high birth weight (>4000 g) are important factors leading to pudendal nerve injury (Snooks et al, 1986; Handa et al, 1996; Brown and Lumley, 1998; Rortveit et al, 2003). Interestingly, postpartum innervation of the external anal sphincter may be damaged by vaginal delivery but not by cesarean section.

In women with stress incontinence it is thought that there is some degree of sphincter weakness in all cases. The female urethral sphincter abnormality can be thought of as a spectrum from a mild weakness that is destabilized by urethral hypermobility (urethral support defect), and the woman leaks only when the urethra moves, from activity like coughing or running, to the severe urethral defect, where urethral support does not play any role, a condition called intrinsic sphincteric deficiency (ISD).

In 1980 McGuire and colleagues first introduced the concept of intrinsic sphincteric deficiency (ISD), an intrinsic malfunction of the urethral sphincter, regardless of its anatomic position. Contemporary theories suggest that all patients with sphincteric incontinence have some degree of ISD. Considerations that support this theory include the fact that the normal urethra is intended to remain closed no matter what the degree of stress or rotational descent. Furthermore, many women with urethral hypermobility remain continent (Versi et al, 1986). Finally, urethral hypermobility and ISD may (and often do) coexist in the same patient. Because urethral hypermobility and ISD often coexist, we believe that they do not necessarily define discrete classes of patients (Nitti and Combs, 1996; Fleischmann et al, 2003). Thus these parameters may be used to

characterize incontinence but not necessarily classify patients. It is recommended that rather than “classifying” stress incontinence, it makes more sense to simply characterize it by two parameters—the degree of urethral mobility and sphincter strength.

Women with ISD have severe leakage, often leaking with minimal or no movement, almost continuous leakage. Urethral hypermobility and support defects in women are most commonly associated with pregnancy and vaginal delivery, pelvic surgery, and chronic abdominal straining (e.g., chronic coughing or constipation). ISD is typically seen after some type of event that damages the urethral closure mechanism, including prior surgery, radiation therapy, neurologic disease or rarely, trauma, and is discussed further below.

Several conditions are associated with ISD in women:

1. Previous urethral or periurethral surgery (e.g., anti-incontinence surgery, urethral diverticulectomy) secondary to periurethral fibrosis, scarring, or denervation (Haab et al, 1996). Prevalence of ISD after two or more failed anti-incontinence operations was found to be as high as 75% (McGuire et al, 1980).
2. Neurologic injury may cause ISD. Sacral neurologic lesions have a variable effect on the bladder and urethral sphincter, depending on the how the neurologic injury affects the parasympathetic, sympathetic, and somatic systems (Gerstenberg et al, 1980; Blaivas and Barbalias, 1983; Wheeler et al, 1986; McGuire et al, 1988). Sacral neurologic lesions may be seen with herniated disks, diabetic neuropathy, multiple sclerosis, spinal cord tumors, and also after extensive pelvic surgery such as abdominoperineal resection of the rectum and radical hysterectomy (Gerstenberg et al, 1980; Blaivas and Barbalias, 1983; Chang and Fan, 1983; McGuire et al, 1988).
3. Pelvic radiation therapy may cause damage to the mucosal seal of the urethra and regional neurovascular structures (Haab et al, 1996).

A clinically important observation is that the woman with a severely damaged urethral sphincter (ISD) may or may not have a hypermobile urethra. As we will discuss, the presence of mobility is critical in the thought process of selecting treatment. If the urethra is mobile, a tension free sling is an option. If the urethra is not mobile, a compressive sling is an option. These are very different surgical procedures with different complication profiles and patient outcomes. However, the overwhelming majority of women we see with SUI have a hypermobile urethra making a tension free sling a viable surgical option. The concept and clinical importance of hypermobility is so important, that when the NIH UITN designed two large prospective surgical trials for SUI, a critical inclusion criteria was that the urethra be hypermobile.

The Hammock Hypothesis

This critical concept helped philosophically sway clinicians towards sling surgery as logical management for SUI. The commonly held view of the pathophysiology of stress incontinence is based on the presence of urethral hypermobility. Normal vaginal wall has support that allows the urethra to compress against the normal vaginal wall, the hammock hypothesis (DeLancey, 1994). In this model, it is the stability of this supporting layer rather than the position of the urethra that determines stress continence.

Urethral support is supplied by connective tissue and muscle arranged to create the hammock that resists the downward pressure created by increases in abdominal pressure. The urethra is supported by the anterior vaginal wall, and is connected to the levator ani muscle complex and arcus tendineus fascia pelvis (ATFP).

The ATFP is a fibrous fascial band that stretches from the pubic bone anteriorly to the ischial spine. The fascial covering of the levator ani consists of two leaves: the endopelvic fascia (abdominal side) and the pubocervical fascia (vaginal side). The two leaves fuse laterally to attach on to the ATFP, creating a hammock of

support under the urethra and bladder neck. Normally, with rises in intra-abdominal pressure, the urethra is compressed against the hammock of supporting structures, which act like a backboard and prevent loss of urine (DeLancey, 1997).

When the supporting structures fail, there can be rotational descent of the bladder neck and proximal urethra during increases in abdominal pressure. If the urethra opens concomitantly, SUI ensues. These findings have important clinical implications that support the contention that the primary goal of surgery for sphincteric incontinence in women is to provide a backboard against which the bladder neck and proximal urethra can be compressed during increases in abdominal pressure. This mechanism describes exactly how a sling procedure works, we are strengthening / replacing the hammock. Observations that we will refer to repeatedly in this report include that the classic fascial pubovaginal sling is located at the bladder neck, is anchored in a fixed position and is compressive. This results in a specific set of complications that adversely affect patient outcome and satisfaction. The midurethral mesh sling is in the midurethra, is not anchored, is tension free and is not compressive, and minimizes these complications, improving patient outcome and satisfaction.

Zaccharin in the 1960s and DeLancey in the 1990s (Zaccharin, 1968; DeLancey, 1994) demonstrated the importance of the pubourethral ligaments and their function in maintaining urinary control under stress circumstances. These findings further demonstrate the fact that hypermobility is a secondary finding noted in association with incontinence but not causative of SUI.

Petros and Ulmsten (1993), furthering these theories, proposed a unifying concept now known as the midurethra theory or integral theory. They felt that pelvic floor injury arising from surgery, vaginal delivery, aging, or hormonal changes lead to weakening or damage of the pubourethral ligaments, impairing the midurethral sphincter mechanism and anterior urethral wall support, and

results in SUI. They theorized that this damage was not only a ligamentous injury but also a weakening of the pubococcygeal muscles at the level of the midurethra. It has been shown that weakness of soft tissue in this area and specifically connective tissue can contribute to urinary incontinence (Ulmsten et al, 1987).

History and Development of SUI Surgery

A common theme we have been discussing is the fact that most women have a hypermobile urethra as an underlying factor causing / contributing to their urine leakage. Surgery to repair SUI includes the bladder suspension procedures that reduce the urethral movement by "suspending" the urethral valve, or a sling procedure that provides a back-board of support, replacing the "hammock" under the urethral valve for compression or kinking. The presence or absence of urethral hypermobility, as I have mentioned, has become the dominant preoperative clinical observation in women with SUI to drive clinical decision-making.

When either bladder suspension or sling procedures are done for SUI, there are three undesirable outcomes. The surgery does not work resulting in continued SUI, the patient has new or worsening urgency symptoms, or the patient has a procedure that is "too tight" resulting in the inability to urinate and requiring the patient to perform self catheterization.

Surgical procedures chosen by expert clinicians are a result of the surgeons knowledge and experience in evaluating the success of the procedure for cure / improvement of SUI as well as the risks and complications of the surgical procedure itself. The surgical procedures discussed in this report will be framed by their efficacy, surgical risk and adverse outcomes, specifically the risk of new or worsening urgency and obstructed voiding. Technical problems that individual surgeons may have when performing suspension or sling surgeries, such as bladder or bowel injury, will be discussed in a later section.

Since the inception of the Pubo Vaginal Sling (PVS) more than a century ago, experimentation has continued with different slings, different materials and different suspension techniques. Materials used for slings include autografts, allografts, xenografts, and synthetics.

Methods of anchoring and location of sling placement have also changed. Sling placement was classically described at the level of the bladder neck. This bladder neck location is a critical difference between the classic fascial sling and the mid urethral slings.

Concept of midurethral sling / tension free

As early as 1990 Petros and Ulmsten developed the Integral theory of female urinary continence. This is an integrated system of ligamentous, fascia and muscular attachments that provided support and function of urinary continence. They demonstrated that the pubourethral ligament serves as a hammock, the normal intact female anatomy of the mid and distal female urethra compresses the urethra during straining /physical activities. The hammock / pubourethral ligament needs to be anchored / secure for this process to work.

This “hammock” is complicated. During straining / exertion, the distal urethra is pulled forward against the PUL for “urethral closure”, prevent leakage. However, during voiding, the distal urethral closure mechanism relaxes, and posterior muscle forces that allow the urethra to open and for urine to flow much easier, resulting is voiding. It was this anatomic and functional understanding of the normal female continence and voiding mechanism that helped surgeons understand the standard surgeries for UI that they were doing at that time. Importantly, this also explained to surgeons the troubling complications they observed.

Concurrent to this improved anatomic understanding of urinary control and incontinence was the recognition that a hypermobile urethra was most common, and was important for the initiation of voiding. Surgery should minimize the effect on hypermobility. The proper placement of a mesh mid-urethral sling was recognized as tension free under the urethra, taking advantage of the hypermobility of the urethra. The mobile urethra will compress against the loose, tension free sling, leading to the term “Dynamic Kinking” that was adopted as a descriptor of the mid-urethral sling mechanism of action. This was different from the historic gold standard fascial sling, placed at the bladder neck. The fascial sling is compressive and does not rely on dynamic kinking. A sling that is compressive provides continuous closure pressure on the urethra, a good thing for reducing leakage from a weakened urethral sphincter mechanism, but potentially a bad thing when urethral compression leads to bladder obstruction and difficulty voiding. Bladder obstruction also leads to bladder urgency symptoms, a critical issue since urgency symptoms are one of the most common reason for patient- reported poor outcome / dissatisfaction after sing surgery.

This mechanism has been confirmed by pre and post operative urodynamic studies (UDS) published by the Urinary Incontinence Treatment Network. UDS are complicated functional testing of bladder muscle function and urethral sphincter function that provides information on the reason for urine leakage, and also evidence of bladder obstruction.

Simply, we are measuring how well the pump (bladder) pumps, and whether there is leakage from or some blockage of the outflow tube (urethra). We know that if the bladder pump is blocked, like any good muscle in your body when up against some resistance, pushes harder, creates more pressure. We can measure this pressure, and from large population studies we know what normal and abnormal are. We can also measure the flow of urine out of the tube. If the flow is normal, we observe there is no blockage, and if the flow is weak, there may be blockage. When we combine the bladder pressure data (how hard the

bladder is pushing) with the flow data we can make observations of whether the patients tube is blocked or not.

The UITN studied women before and after colposuspension, fascial bladder neck sling and mesh mid urethral sling surgery. Importantly, we found that women with the surgery that did not work so well (Burch suspension), there was little evidence of obstruction. Remember, the Burch patients had little clinical problems with bladder obstruction after surgery, had little urinary retention, did not need to be loosened, etc. The fascial bladder neck sling patients had a much higher rate of urinary retention and reoperation for obstruction (a surgery that was too tight), and on testing we observed significantly higher bladder pressures and lower urine flow rates confirming that the mechanism of action of these slings is compression / obstruction. Remember, that compression / obstruction also has increased rates of urgency.

The UDS evaluation of the mesh midurethral slings (transobturator and retropubic) was very important. Though they had the same efficacy as the fascial bladder neck sling (better than the Burch BNS), they did not result in elevated bladder pressures, confirming that they are not obstructive (unless placed too tight, a technical issue) but instead do work through the “dynamic kinking” mechanism. The mesh MUS was not compressive and obstructive. This minimizes the obstruction and urgency symptoms that worsen patient outcome.

Surgical Procedures for SUI

Colposuspension

Colposuspension is a term describing surgery to reduce urethral hypermobility. These surgeries involve placing sutures in the anterior vaginal wall / fascia, elevating the anterior vaginal wall / fascia to provide compression of the urethra and reduce urine leakage. These procedures are done from the abdominal or vaginal approach.

Burch / Marshal Marchetti Kranz (MMK) procedures. These surgeries were considered the gold standard approach for SUI for decades. They required an abdominal incision, important because this introduces risk of incisional hernia, nerve entrapment, post operative pain, and 4-6 week recovery and all of the attendant loss of work / normal activity. These are much more invasive than a mesh MUS.

The suspending suture is placed in attenuated vaginal wall tissue (which is why the patient has SUI to begin with) and then secured to a fixed point, either the inferior pubic ramus (MMK) or to coopers ligament lateral to the pubic ramus (Burch). Though data shows bladder suspension procedures are inferior to the fascial sling procedures for cure of SUI, patients report similar quality of life and satisfaction between the fascial sling and Burch BNS. Why is this? Likely because the fascial sling procedure, placed at the bladder neck is more compressive and therefore has more bladder obstructive symptoms causing difficult urination and urgency symptoms. These issues lead to patient dissatisfaction.

Sling procedures

Sling Materials

There have been many different materials used for sling. The ideal material provides long-lasting suburethral support with minimal complications. Ideally, implanted material should be incorporated into the host with minimal tissue reaction. In reality, most materials promote organized fibrosis, reinforcing the sphincteric mechanism through improved suburethral support. Theoretically, a greater degree of fibrosis leads to better clinical results (Bidmead and Cardozo, 2000; Woodruff et al, 2008). Yet, inflammatory infiltration leads to rapid sling material degradation and possible tissue destruction with erosion (Bidmead and Cardozo, 2000). Although there is complete biocompatibility of the autologous sling and negligible urethral erosion, biologic and synthetic graft materials have

been increasingly used to decrease operative time, morbidity, pain, and hospital stay (Niknejad et al, 2002).

Autologous. The most commonly used autologous materials include rectus fascia and fascia lata. Rectus fascia is harvested through a suprapubic Pfannenstiel incision. FitzGerald and associates (2000) reported that after sling placement, rectus fascial grafts undergo extensive remodeling with increased fibroblasts and connective tissue. Yet, histologic comparison of PVS grafts noted the greatest degree of host fibroblast infiltration and neovascularization in autologous materials with minimal inflammatory or foreign body reaction. The fascial graft changes were consistently intact with a small amount of sling degradation at explantation up to 65 months after placement (Woodruff et al, 2008). The benefits of autologous tissue include the lack of tissue reaction and negligible urethral erosion (Webster and Gerridzen, 2003). Disadvantages include increased operative time and hospital stay, relative increase in postoperative pain, suprapubic tissue seroma formation and hernia formation in a rectus fascial PVS (Gomelsky et al, 2003).

Fascia lata is the other commonly utilized autologous material for a PVS. It is harvested from the thigh and has similar properties to rectus fascia (Beck et al, 1988; Latini et al, 2004). Like rectus fascia, fascia lata is completely biocompatible and has minimal tissue reaction. The recovery time may be less, and there is no risk of future abdominal hernia formation, unlike rectus fascia. Yet, fascia lata requires repositioning of the patient, increased operative time, and operating in an area unfamiliar to urologists (Govier et al, 1997). Wheatcroft and colleagues (1997) reported 67% of their patients had pain on walking for 1 week after surgery. Latini and coworkers (2004) only reported 7% of patients with pain at incision site 1 week postoperatively after using a Crawford fascial stripper. Debility from a thigh hernia has also been reported.

Raz and associates (1989) described use of in-situ vaginal wall for autologous

sling. This tissue may lack sufficient tensile strength, and there is a risk of epithelial inclusion cyst formation and possible vaginal shortening. Lack of retropubic space dissection may decrease the overall efficacy of this procedure secondary to less scarring (Raz et al, 1989; Ghoniem and Hassouna, 1998; Loughlin, 1998; Appell, 2000).

Allograft. Biologic and synthetic graft materials have been increasingly used to decrease operative time, morbidity, pain, and hospital stay. Cadaveric allografts have been used in many nonurologic surgical arenas (e.g., orthopedics, neurosurgery) and eventually adopted for SUI. Allograft slings include cadaveric fascia lata or acellular human dermis.

After harvest the allografts are processed by solvent dehydration or by lyophilization (freeze-drying) to remove genetic material and to prevent the transmission of infectious agents. Secondary sterilization may also be achieved by gamma radiation (Gomelsky et al, 2003). Histologic analysis reveals cadaveric dermis to have little host fibroblast infiltration and little neovascularity, particularly in central aspects of the graft. Additionally, inconsistencies were found within the materials grossly, with specimens exhibiting significant thinning and degradation of the graft, disrupting the sling scaffold (Woodruff et al, 2008). No specific allograft has shown a clinical advantage in use.

Biomechanical studies have shown that solvent-dehydrated cadaveric fascia lata and acellular dermis have a higher maximal load failure compared with freeze-dried cadaveric fascia lata (Hinton et al, 1992; Lemer et al, 1999). Lemer and associates (1999) prospectively studied the maximum load failure and stiffness of rectus fascia versus freeze-dried fascia versus solvent-dehydrated fascia and cadaveric dermal grafts. The mean values for maximum load to failure, maximum load-graft width, and stiffness were all significantly lower for the freeze-dried fascia lata group compared with the autologous, solvent-dehydrated, and dermal graft groups.

Although biomaterials were thought to be a good choice for increased biocompatibility, lower risk of erosion, and lack of response to hormonal stimuli, allografts raise the concern of potential transfer of disease, including human immunodeficiency virus (HIV), hepatitis, and Creutzfeldt-Jacob prion infection. There has been one documented case of HIV transmission from a tissue transplant since the onset of screening in 1985. The estimated risk of acquiring tissue from a properly screened donor infected with HIV is 1 in 1,667,600 (Gallantine and Cespedes, 2002). A few cases of Creutzfeld-Jakob disease (CJD) have been reported after transplantation of cadaveric dura or corneas; however, skin obtained from animals infected with prions has demonstrated no detectable infectious particles. Currently, the theoretical risk of developing CJD from a non-neural allograft is 1 in 3.5 million. No cases of hepatitis or CJD have ever been attributed to the use of processed cadaveric fascia or dermis (Amundsen et al, 2000b; Gallantine and Cespedes, 2002). Within the musculoskeletal tissue transplantation literature, two cases of hepatitis transmission have been reported.

In June 2002, the Centers for Disease Control and Prevention (CDC) reported a case of hepatitis C transmission from minimally processed, cryopreserved patellar tendon allograft (CDC, 2003; Vangsness, 2006). Despite the low risk of disease transmission, human DNA has been detected in various allograft materials (Choe and Bell, 2001; Hathaway and Choe, 2002). The clinical significance of this is unknown. The theoretical risk of developing hepatitis from allograft graft material is unknown.

Xenograft Xenografts have been utilized since the 1980s (Descurtins and Buchmann, 1982; Iosif, 1987) because of the easy access and avoidance of fascial harvest. Porcine and bovine xenografts have been used as sling material but have been less popular in recent years. The forms of xenograft available for use are porcine dermis or small intestinal submucosa (SIS) and bovine

pericardium.

There became two concerns with Xenografts, the strength of material after processing and potential transfer of genetic material with human implantation. Modern processing techniques to remove genetic material have made porcine safer and more pliable, yet there is significant loss of tensile strength after implantation in a 12-week rabbit model (Dora et al, 2004). Although SIS was felt to be non-immunogenic, animal studies by Thiel and colleagues (2005) observed an intense inflammatory reaction 30 to 90 days after subcutaneous implantation. Kalota (2004) reported 6 of 18 women experienced postoperative inflammatory reaction after a PVS procedure. Ho and colleagues (2004) reported 6 of 10 women presented with pain and erythema at the abdominal incision, and 2 developed abscesses. All were treated conservatively, except 1 patient who required abscess drainage. The etiology is unknown but may be secondary to a foreign body reaction from the multilayered (8-ply) SIS material, a reactive manufacturing ingredient, or a tendency for suprapubic fat to produce an inflammatory reaction (John et al, 2008).

Histopathologic comparison of sling materials revealed xenograft (porcine dermis) to have no host fibroblast infiltration, no inflammatory reaction, and no foreign body reaction. Xenograft had the highest propensity to encapsulate. A capsule formed around the porcine dermis, isolating the graft from the periurethral tissue. The graft was described as appearing similar to its original appearance at time of implantation (Woodruff et al, 2008).

Importantly, there were several issues that were bothering surgeons; concerns about the strength and integrity of allograft and xenograft, and the concern about transfer of genetic material. At the same time, other surgeons were reporting their experience with the mesh midurethral slings. The excellent results with mesh MUS, the known issues with compressive bladder neck tissue slings combined to dramatically changed surgeon behavior away from tissue slings.

Synthetics

The addition of synthetic material for use in PVS surgery brought obvious advantages: unlimited supply of artificial graft material in endless sizes and shapes, consistency in quality, and elimination of harvest site and decreased associated operative time. As compared with absorbable biomaterials, synthetic materials are more uniform, more consistent, and more durable. On histopathologic comparison, synthetic materials demonstrated the greatest amount of fibroblast ingrowth and tissue ingrowth into the specimen. There is no degradation or disruption of the graft, and the mesh is completely infiltrated by the viable host tissue (Woodruff et al, 2008).

Artificial graft materials do have potential drawbacks, including infection, erosion, or vaginal extrusion. However, wound complications may occur with any SUI surgery as presented in the SISTEr trial. This comparison of the Burch BNS and fascial pubovaginal sling reported wound complications that required surgical intervention including incisional hernia (Burch, 5 patients; sling, 3), seroma or hematoma (Burch, 2; sling, 3), infection (Burch, 2; sling, 2), abscess (Burch, 1; sling, 1), and vaginal wound revision (Burch, 3; sling, 2). There were also wound complications not requiring surgery including 2 sling exposures (visualization of the sling material in the vagina), incisional hernia (Burch group, 2; sling group, 1), superficial wound-edge separation (Burch, 10; sling, 5), seroma or hematoma (Burch, 13; sling, 11), infection (Burch, 31; sling, 21), and granulation tissue or stitch granulomas (Burch, 13; sling, 31).

The chemical and physical properties of each artificial material and patient characteristics determine how the sling is incorporated into the surrounding tissue and its susceptibility to infection, rejection, erosion, or extrusion. The susceptibility to infection in multifilament fibers is proportional to the porosity and the pore size of the materials (Amid, 1997; Niknejad et al, 2002). Tightly woven mesh provides a safe harbor for small bacteria, excluding macrophages and

polymorphonuclear leukocytes. Loosely woven mesh allows tissue ingrowth and neovascularization, without limiting cellular access. Tissue bonding to the mesh strengthens and supports the repair. A tightly woven and large-diameter filament mesh will tend to exhibit increased stiffness or decreased pliability, contributing to migration, extrusion, or erosion. The classification by Amid (1997) used for synthetic materials in hernia surgery may be practically applied to urology as well.

The most commonly utilized synthetic material for a PVS is polypropylene mesh. It is composed of loosely woven strands of synthetic material, with a pore size greater than 80 µm, permitting passage of macrophages that may allow better host tissue ingrowth compared with the smoother, more tightly woven counterparts (Kobashi et al, 2005). This represents type I among the Amid classification. In fact, Amid (1997) concluded that the risk of infection and seroma formation was avoided by utilization of type I prostheses. TVT and TVT-O utilize a macroporous, lightweight monofilament type I mesh which permits passage of these cells and the infiltration of small capillaries leading to a reduced risk of infection and excellent host tissue ingrowth, which is consistent with my clinical experience and the medical literature. This mesh material is the gold standard, standard of care, and has been extensively studied and used by surgeons who treat SUI. (SUFU & AUGS 2014 Position Statement).

Results of pubovaginal sling procedures

The rectus fascial autologous sling has been effective up to 7 years (Howden et al, 2006) postoperatively with low morbidity when performed by experienced surgeons. Cure rates have ranged from 46% to 97%, although the measurement of outcomes is varied. Patient-derived cure rates are lower than physician-based or chart review–based outcomes. There is no direct correlation between universally accepted objective and subjective measures of improvement or cure for antiincontinence procedures (Padmanabhan and Nitti, 2006). The most commonly cited reason for failure relates to urgency symptoms. UUI at follow-up is a common reason for patient dissatisfaction. Reported de novo or UUI rates

are 2.0% to 20.8% (Mason and Roach, 1996; Zaragoza, 1996; Haab et al, 1997;

The SiSTER trial (Albo et al, 2007), a multicenter, randomized clinical trial, compared the rectus fascial autologous sling to the Burch colposuspension. The two primary outcomes were composite measures of success in terms of overall urinary incontinence measures (no self-reported symptoms of incontinence, increase of less than 15 g in pad weight during a 24-hour pad test, and no medical or surgical treatment for incontinence) and of SUI measures (no self-reported symptoms of SUI and negative stress test), specifically. Whereas success rates at 24 months were higher for the PVS (47% vs. 38%, P = .01), voiding symptoms were also higher: urinary tract infections (UTIs) (48% vs. 32%), difficulty voiding (14% vs. 2%, P < .001), and postoperative UUI (27% vs. 20%, P = .04). All of the surgical procedures for bladder outlet obstruction (19 of 20) were performed in the sling group. The rate of UTI's seen at 24 months with mesh midurethral slings in the TOMUS study compare favorably (TVT = 17.4%, TOT = 10.7%) to the fascial pubovaginal sling and Burch procedure reported above (48% and 32%) (Albo, M. J Urol 2012). 5 year extended SISTEr follow up data were published showing no serious adverse events were reported in E-SISTEr. Adverse event rates were similar for the 2 treatment groups with Burch 10% and sling 9%. There were 75 adverse events (Burch 38 and sling 37) in 45 participants (Burch 23 and sling 22). Nearly all events (72/75) were recurrent urinary tract infection (36 events in 21 Burch patients, 36 events in 21 sling patients) (Brubaker, L. J Urol, 2012).

Allograft results

The autologous fascial PVS was the gold standard with proven efficacy but with the morbidity of fascial harvest, cadaveric allograft slings were introduced. This was to provide decreased morbidity, reduce operative time, and minimize pain.

Walter reported on morbidity of harvesting fascia lata from the lateral thigh for pubovaginal sling and noted both short term and long term complications.

Immediate perioperative problems included 10% local wound issues (1% hematoma, 3% seroma and 7% cellulitis requiring antibiotics). Long term issues included 5% with significant symptoms of the donor leg, 13% with unacceptable cosmesis and or leg discomfort (Walter AJ, et al., Am J Obstet Gynecol 2001).

There are limited outcome data and question arouse regarding cadaveric fascia efficacy and durability. Early literature used frozen or freeze-dried cadaveric fascia lata. There were also a variety of sling anchoring methods, including suture and bone anchors (Handa et al, 1996; Wright et al, 1998; FitzGerald et al, 1999; Brown and Govier, 2000; Carbone et al, 2001; Flynn and Yap, 2002; O'Reilly and Govier, 2002; Walsh et al, 2002; Amundsen et al, 2003; Richter et al, 2003; Almeida et al, 2004; Howden et al, 2006). Subsequent reports has shown that tissue processing techniques can harm the sling and result in worse cadaver sling outcome compared to autologous sling procedures (Nazemi et al, 2008). Lemer and associates (1999) found differences in both tissue integrity and durability between freeze-dried fascia and solvent-dehydrated fascia and proposed ice crystal formation with tissue freezing may disrupt the collagen matrices, resulting in poor tissue strength. Failure rates for frozen or freeze-dried grafts range from 6.0% to 37.6% (Handa et al, 1996; Wright et al, 1998; FitzGerald et al, 1999; Brown and Govier, 2000; Carbone et al, 2001; Flynn and Yap, 2002; O'Reilly and Govier, 2002; Walsh et al, 2002; Amundsen et al, 2003; Richter et al, 2003; Almeida et al, 2004; Howden et al, 2006). Interestingly, 2/3 patients who had SUI recurrence were continent after a synthetic midurethral sling. FitzGerald and associates (1999) reported on an early failure rate of 17% in women undergoing cadaveric fascia lata sling. Evaluation of the failed sling material demonstrated disorganized remodeling, areas of graft degeneration, and evidence of immune reaction. They concluded that freeze-dried, irradiated donor fascia lata grafts should not be used for pelvic floor surgery.

Concerns raised in the literature coupled with the consistent success and rapid adoption of synthetic midurethral slings led surgeons to stop using cadaveric

tissue for slings at most centers. Thus there are few data to assess long-term outcomes and define sling outcomes after solvent dehydration techniques (Nazemi et al, 2008).

The failure with cadaveric fascia lata prompted many to change sling materials to the newly available cadaveric dermal grafts. Crivellaro and associates (2004) presented their prospective series of patients treated with bone-anchored Repliform cadaveric human dermal allograft (LifeCell Corp., The Woodlands, TX) PVS. There was a 22% failure rate, yet based on patient report there was average incontinence improvement at 9 months of 85% and at 18 months of 80%. The 2 patients requiring long-term intermittent catheterization had neurogenic bladders.

Owens and Winters (2004) assessed outcome and patient satisfaction with Duraderm allograft (C.R. Bard, Covington, GA). Initial results were promising, with a dry rate of 68% and improved rate of 24%. At intermediate follow-up only 32% of the patients were dry and 36% noted improvement. Surgical reexploration revealed almost complete absence of graft material, without evidence of infection or excessive inflammatory response.

Xenograft results

A number of different sling materials are available and have been discussed. Because of the morbidity of autologous fascial harvest and high failure rates of allograft materials xenografts were an attractive option. They are associated with a low rate of infection, rejection, or extrusion, owing to their incorporation into host tissue (Rutner et al, 2003). Pelvicol, SIS, and bovine dermis are the xenografts used in PVS surgery, with cure rates of 31% to 93.4%. In randomized trials, porcine dermis was associated with significantly inferior long-term cure rates compared with the autologous PVS (Arunkalaivanan and Barrington, 2003).

Voiding problems after pubovaginal sling

The voiding problems that are observed after PVS are a major issue that drove surgeons to adopt the midurethral mesh sling technique. Remember that the fascial PVS is located at the bladder neck, and is compressive, both associated with the obstruction and it's sequela observed. Two dominant clinical problems are created by iatrogenic obstruction, urgency and urge incontinence, and obstructive voiding with decrease stream, straining, and incomplete emptying. This second issue is felt to be related to an increased urinary tract infection rate. The incidence of voiding dysfunction after continence surgery varies widely in the literature, from 2.5% to 35% (Foster and McGuire, 1993; Carr and Webster, 1997; Cross et al, 1998; Chaliha and Stanton, 1999).

The literature is full of examples demonstrating a difference in obstruction and urgency depending on the SUI procedure done. The fascial PVS has higher rates of voiding dysfunction than the Burch colposuspension UITN (Stanton et al, 1983). A pivotal study, the SISTEr trial, a multi institutional, randomized clinical trial comparing autologous rectus fascia PVS and Burch colposuspension showed that although the SUI success rate was higher for women who underwent the fascial sling procedure there was significantly greater voiding dysfunction (63% vs. 47%, $P < .001$): UTIs, difficulty voiding, and postoperative UUI (Albo et al, 2007). A meta-analysis by the AUA Stress Urinary Incontinence Clinical Guidelines Panel reported that the incidence of urinary retention more than 4 weeks after PVS placement was 8% and the risk of permanent retention "generally does not exceed 5%" (Leach et al, 1997). In 2010, an updated AUA guidelines panel reported urinary retention after fascial pubovaginal sing lasting more than 1 month at 8%, and for synthetic midurethral sling at 3%. This improvement in urinary retention rates with the mesh midurethral sling was felt by the guidelines panel to be important (Dmochowski et al, J Urol, 2010). Historically it was felt that patients who had urinary retention after fascial sling may have had some degree of poor bladder function pre-operatively. However, most now believe that obstruction after a fascial sling more commonly relates to

technical factors (i.e., placement and tension of sutures or sling material). When there is an inadequately supported bladder neck/ proximal urethra there is potential for continued SUI. When the sling is tied too tightly there is excessive compresion of the bladder neck and proximal urethra.

Though poor bladder function may be present preoperatively, it is unusual in neurologically normal women. It is widely believed now that in neurologically normal women who could not void well after fascial slings that the slings were too tight. If the sling was aggressively loosened in the early post op period the patient had high probability of recovering spontaneous voiding. This belief was reinforced by our experience with the mesh MUS, where it is now common practice to quickly loosen or revise a sling in a woman who is not voiding spontaneously. In fact, it is my practice loosen or modify a mesh MUS within 4-7 days for obstructive voiding symptoms in the office. This cannot be done with any bladder suspension or fascial sling.

Why The Rapid Adoption of the Mesh Mid Urethral Sling?

A literature review by Cox et al (Nature Reviews, Urology Vol 10, Feb 2013) provides an argument why the mesh midurethral slings have become the gold standard, “The traditional gold standards of Burch retropubic colposuspension and pubovaginal slings are still appropriate treatment options for some patients, but randomized controlled trials have demonstrated that synthetic midurethral slings are just as effective as these traditional procedures but with less associated morbidity. Thus, midurethral slings— inserted via a retropubic or transobturator approach—have become the new gold standard first-line surgical treatment for women with uncomplicated SUI.”

The following discussion will outline in the many years of experience, trials and data that convinced surgeons from around the world to use midurethral slings as

the preferred first line surgery for SUI.

TVT

The TVT procedure was developed using the concepts of the hammock hypothesis and the integral theory. The goal is a minimally invasive approach, to support a weakened midurethral mechanism with an improved material that will support the ingrowth of new host tissues and provide long term support.

The TVT procedure was described as done under local anesthesia to allow intraoperative stress test and confirm procedural efficacy. Polypropylene monofilament mesh was chosen for several reasons. The material allowed migration of host inflammatory leukocytes and macrophages into the mesh for control of infection and to promote host wound healing. This material was optimal for inciting fibrous tissue ingrowth. Further discussion of the mesh and its characteristics are deferred to the material experts. However, as a busy clinician, who has implanted thousands of mesh slings and other mesh products, I have yet to observe a single polypropylene mesh infection, but have observed infection with Ob-tape and bovine pericardium.

Results of TVT

Many reports evaluate the outcomes of the mesh midurethral sling. Limitations include that outcomes are reported using different tools, lengths of follow-up, and overall definitions of success and failure. However, there are some consistencies that are observed through out many studies. In addition, there are now large, multicenter studies that provide generalizable data.

Initial results with the midurethral sling technique approximated 80% (author-defined) success rates (Ulmsten et al, 1996). A subsequent prospective multicenter trial that included 130 women with genuine SUI who were observed for 1 year revealed success rates of 91% (Ulmsten et al, 1998). Seven percent were considered improved, and only 2% were deemed failures. Complication

rates were low, including one bladder perforation and one wound infection. Voiding dysfunction was also relatively low, with 1 patient experiencing retention for 12 days, which resolved spontaneously, and 3 patients with less than 3 days of voiding dysfunction.

Nilsson and Kuuva (2001) evaluated 161 consecutive women after TVT in mixed population including 28% who had failed prior incontinence surgery, 11% had ISD, and 37% had MUI. At 16 months mean follow-up, the overall objective cure rate was 87%, with 7% significantly improved and another 5% considered failures. Bladder injury rate at the time of insertion was 3.7%, and 4.3% of women experienced short-term de novo voiding dysfunction. Urgency symptoms arising after surgery occurred in 3% of women, yet 80% of the women who had preoperative urgency symptoms had relief of those symptoms at their 16-month visit. This was the first time we observed several of the advantages of mesh MUS; good SUI treatment rates, decreased obstruction, decreased urgency and high patient satisfaction. Though different surgeons and centers reported slightly different numbers, the results were overall consistent. The mesh MUS was clearly getting the attention of surgeons around the world. As I spoke with my colleagues around the country, and at national meetings, we all were very interested in this new sling technique.

Ulmsten and associates (1999) reported an 86% success rate in 50 women at 3 years. Olsson and Kroon (1999) reported 90% success in 51 women at 3 years. Doo (2006) reported overall 5-year success rate was 94.9%, with an 86.6% patient satisfaction rate. Although success rates between 1 and 5 years were similar (97.7% and 94.9%), the cure rate decreased from 90.1% to 76.9%. Nilsson reported on a 3 center study of 90 women and reported success rates of 84.7% at 5 years (Nilsson et al, 2001) and 81.3% at 7 years (pad test diary, QOL VAS, subjective questionnaire) (Nilsson et al, 2004). Liapis and colleagues (2008) prospectively assessed the efficacy of the TVT in 65 women: at 5-year follow-up the objective cure rate (UDS, pad test, symptom questionnaire) was

83% and failure rate was 9.4%, whereas at 7-year follow-up the objective cure rate was 80% (stress test, symptom questionnaire) and the failure rate 13.5%. Song and associates (2009) reported on ≥7 years follow-up in 306 women with a cure rate of 84.6%; they reported on 6 patients who had complications from mesh exposure. As a continuation of their earlier work, Nilsson and coworkers (2008) provided 11 year follow-up in a prospective observational cohort study of 90 women with primary SUI. Ninety percent of these women were objectively cured, and 77% reported subjective cure (pad test, a stress test, physical examination, VAS. Patient's global impression of cure, and condition specific quality of life questionnaires). No late onset adverse effects or cases of mesh erosion were seen. Long term follow up are presented below

TVT vs. Other SUI Surgery

Ward and Hilton compared the TVT versus Burch procedure with short (Ward and Hilton, 2002), intermediate (Ward and Hilton, 2004), and long-term (Ward and Hilton, 2008) follow-up. 344 women were randomized to either TVT or Burch, with no significant difference in cure rates at 6-month follow-up. TVT was associated with more operative complications (i.e., bladder injury), yet colposuspension was associated with more postoperative complications and longer recovery (Ward and Hilton, 2002). At 2-year follow-up, overall cure rates noted in the study were lower than other reported cure rates, with 63% of TVT patients and 51% of Burch patients cured. This is an example of how methodology can influence cure rates, this study used a strict definition of cure (1-hour pad test with change in weight <1 g) and failures including both dropouts and those lost to follow-up. There were significantly more patients in the colposuspension group needing intermittent self-catheterization (<0.0045) and surgery for pelvic organ prolapse (<0.0042) than in the TVT group (Ward and Hilton, 2004). At 5 year follow-up there were no difference in cure rates. Consistent with earlier studies, prolapse was seen more commonly in the Burch group. Two tape extrusions (only one symptomatic) were found in the TVT group. Unlike reports of 27% de novo urgency and UUI in the literature (Jarvis, 1994)

after colposuspension, this group reported less than 2% after TVT and less than 5% after colposuspension (Ward and Hilton, 2008).

Ward and Hilton (2002) and El-Barky and colleagues (2005) found operation time, hospital stay, and time until return to normal activity significantly shorter in the TVT group. El-Barky and colleagues (2005) reported two bladder perforations in the TVT group (<0.05), but wound infections (<0.05) were more common in the Burch group. Bai and associates (2005) compared TVT with Burch and fascial sling: at 3- and 6-month follow-up there were no differences in cure rates between the operations, but at 12 months the patients with a PVS had significantly higher cure rates (92.8%) than those who had the colposuspension (87.8%) or the TVT procedure (87.0%). Wadie and associates (2005) found PVS and TVT procedures to be equally effective. The TVT procedure is cost effective and superior in terms of impact on health care spending compared with open colposuspension (Manca et al, 2003).

A Cochrane review presented nine trials that compared mesh MUS vs. the Burch procedure (Ogah 2011). Within the first 12 months after surgery, the cure rates were 79% (310/392) with mesh MUS and 82% (277/337) with Burch procedure. these were not statistically significantly different (RR 0.96, 95% CI: 0.90--1.03)

Eight trials compared the results of mesh MUS vs laparoscopic Burch (Ogah 2011). The combined results from six trials showed no statistically significant difference in the reported cure rate between minimally invasive synthetic suburethral sling operations and laparoscopic colposuspension within 12 months (80% vs. 74%, RR 1.11, 95% CI: 0.99--1.24; Fig. 4).

These trials noted no other apparent differences between techniques other than that the TVT group recovered more rapidly and had a lower need for subsequent urogenital prolapse procedures than the Burch group.

Complications were similar between TVT and Burch colposuspension, with the exception of bladder perforation (higher in TVT group) and reoperation rate (higher in the Burch colposuspension study arm).

Mesh MUS Versus Traditional Fascial Sling

The Cochrane review presented nine trials that compared mesh MUS and fascial pubovaginal sling (Ogah 2011). There was no statistically significant difference between the subjective cure rates at 1 year: 75% (237/316) for mesh MUS versus 71% (201/283) for fascial sling [risk ratio (RR) 1.03, 95% confidence interval (CI): 0.94--1.13].

TVT: "Bottom-UP" vs. "Top-Down"

The TVT is a "bottom-up" procedure, the surgeon exposes the urethra vaginally then places the trocar from the vagina behind the pubic bone to exit through the skin in the supra-pubic skin. An alternate technique is to expose the urethra vaginally, then place trocar from the supra-pubic skin site behind the pubic bone to exit through the vagina. This "top-down" approach and was called the suprapubic arc sling (SPARC). Five trials have compared TVT to SPARC. Based on both subjective and objective cure rates, women were statistically significantly more likely to be cured with the bottom-up TVT [e.g., subjective cure rate 85% vs. 77% with top –down SPARC, RR 1.10, 95% CI: 1.01--1.20]. In addition Women having the bottom-up TVT approach reported fewer adverse effects (bladder perforation, vaginal erosions; voiding dysfunction; and tape erosions) than with the top-down SPARC.

TVT was compared to the intravaginal sling (IVS), a multifilament, miniporous polypropylene tape material produced by Tyco that is passed similar to a SPARC. Rechberger and associates (2009) reported no differences in cure rates at 13-month follow-up of 50 patients per group. Complications were similar with the exception of postoperative acute urinary retention occurring significantly more commonly among the patients having the TVT procedure. Meschia and

colleagues (2006) compared the TVT and IVS with intermediate follow-up and reported subjective cure rates of 80% (TVT) and 78% (IVS) and objective cure rates of 85% (TVT) and 72% (IVS). However, Eight (9%) of the IVS patients experienced vaginal erosion, with none found in the TVT group. The TVT was compared with the IVS and SPARC by Lim and associates (2005) in the SUSPEND trial. There was no significant difference between the cure rates: 87.9% (TVT) versus 81.5% (IVS) and 71.4% (SPARC). But there was a significantly greater rate of tape extrusion in the SPARC group. Importantly, Balakrishnan and coworkers (2007) followed a subgroup of IVS patients from the Lim and associates' (2005) group up to 30 months and found 13% with sling erosions, requiring removal of the sling. Of the 29 patients (47%) from this initial IVS group seen 12 to 34 months postoperatively, 24% experienced sling erosion with associated sinus formation, requiring sling removal.

Development of the Transobturator Sling Midurethral Sling

The mesh MUS was showing promise as being as effective as the Burch and fascial sling procedures, yet had potential complications of abdominal / retropubic / retroperitoneal organ injury with needle passage. These concerns drove the development of sling placement via the obturator foramen that should reduce / eliminate the possibility of adjacent bladder, vascular or bowel injury. Delorme presented the TO sling in 2001 and published a series in 2003 (Delorme 2003).

An important observation of the TO sling is that the mesh vector closely followed the anatomic path of normal structures supporting the midurethra. The TO vector was very different from the more vertical RP sling vector, the TO sling is adjacent to the urethra only at the bottom, and does not compress the sides of the urethra as a RP sling does. Surgeons considered this and thought two things. First, the TO sling may not be as tight, an advantage in that the TO sling may not cause as much obstruction or urgency as a RP sling. Remember that the complications of SUI surgery being "too tight", obstruction and urgency, remained an important consideration when evaluating overall patient outcome. This consideration is

what drove me to adopt the TO sling as my first choice sling in uncomplicated women. Second, some thought the TO sling may not work as well, it may not be tight enough for women who have worse urine leakage from poor urethral function.

Over the next several years several studies were developed to compare the TO and RP sling procedures. The landmark study was the NIH funded multicenter TOMUS trial (Richter), the 24 month follow up (Albo) and the 5 year follow up being prepared now for publication (Kenton), which included TVT as the retropubic device and TVT-O and one of the transobturator devices. These trials reported several important additions to the literature. The 24 month trial reported that of the 597 women 516 (86.4%) were assessed. Objective success for RP and TO mid urethral slings were 77.3% and 72.3%, respectively and subjective success rates were 55.7% and 48.3%, respectively. Patient satisfaction (RP 86.3% vs TO 88.1%, p = 0.58), frequency of de novo urgency incontinence (RP 0% vs TO 0.3%, p = 0.99) and occurrence of mesh exposure (RP 4.4% vs TO 2.7%, p =0.26) were not significantly different. The RP mid urethral sling group had higher rates of voiding dysfunction requiring surgery (3.0% vs 0%, p _ 0.002) and urinary tract infections (17.1% vs 10.7%, p _ 0.025), whereas the TO group had more neurological symptoms (9.7% vs 5.4%, p _ 0.045) (Albo). Kenton's 5 year data manuscript is in development and may be available for discussion in the near future.

TO Slings: Inside Out vs. Outside In

Two types of TO sling have been performed, the inside-out (TVT-O) [De Leval J. Novel surgical technique for treatment of female stress urinary incontinence: transobturator vaginal tape inside-out. Eur Urol 2003;44:724–30.] and the outside-in transobturator tape (TOT) [Delorme E. Transobturator urethral suspension: mini invasive procedure in the treatment of stress urinary incontinence in women. Prog Urol 2001;11:1306–13.] approaches, with the choice of the surgical approach predominantly driven by surgeon preference.

Abdel-fattah (European Urology, 62(2012)843–851) reported A 3-yr follow-up study of the Evaluation of Transobturator Tapes (E-TOT) trial, a randomised controlled trial (RCT) conducted with women undergoing TO-TVT as a sole procedure between April 2005 and April 2007 in a tertiary urogynecology centre in the United Kingdom. The 3-yr follow-up was completed by 238 of the 341 women (70%). The overall success rate, based on Patient's Global Impression of Improvement response, was 73.1%, with no significant difference between the inside-out and the outside-in TO-TVT (73.18% vs 72.3%; odds ratio: 0.927; 95% confidence interval, 0.552–1.645; p = 0.796). Compared with the 1-yr follow-up, there was a significant reduction in the patient-reported success rate (p = 0.005); however, no independent risk factors were identified. A clinically significant improvement (≥10 points) was seen in 80% (n = 191) of women, with no significant difference between both groups (p = 0.113). Twenty-two women (6%) underwent further surgical treatment within 3 yr. The lack of an objective outcome assessment is a potential limitation of this RCT.

Long Term Follow up after mesh MUS

Long-term results mirror the short-term experience with this procedure. Study methodology influences the results reported, but certain trends persist. Cure rates remain high, though strict cure rates decline in some studies with time. However, satisfaction rates remain high. Most of us believe that patient satisfaction is the most important outcome measure, since satisfaction measures not only improvement of SUI symptoms but also the presence of obstructed voiding and urgency symptoms. Urgency symptoms remain complicated because they may pre-date the index surgery and may develop over time as a woman ages. The observation that there is less urgency after mesh midurethral slings is an important clinical point.

Svenningsen (Int Urogynecol J 2013) reported on 10 year follow up after TVT. They included 483 women; 327 attended a clinical follow-up consultation and 156

had a telephone interview. Median duration of follow-up was 129 months. Objective cure rate was 89.9 %, subjective cure rate was 76.1 %, and 82.6 % of the patients stated they were “very satisfied” with their surgery (treatment satisfaction rate). Only 2.3 % of the women had undergone repeat SUI surgery. Subjective voiding difficulties were reported by 22.8 %, the majority describing slow stream or intermittency. De novo urgency incontinence increased significantly from 4.1 % 6–12 months after surgery to 14.9 % at the 10-year follow-up. Though they seemingly report a high subjective rate of voiding difficulties (22.8 %), the most common symptom was slow stream or intermittency. These symptoms did not bother the women, nor was there objective data to show obstruction. The percentage of women stating they were “very satisfied” with the treatment was similar for the women reporting voiding difficulties and those reporting no such problems (83.2 % vs 82.3 %, p=0.84). Furthermore, there was no difference in objectively low urinary flow (Qmax<15 ml/s) at the 10-year follow-up between the groups (27.7 % vs 27.1 %, p=0.92). Importantly, they report only 1 case of asymptomatic mesh exposure found at the 10-year follow-up. In addition to the 3 mesh exposures that had previously been surgically managed (total of 4 or 0.8 % with mesh exposure).

Consistent with our observations that urgency symptoms greatly affect SUI surgical outcomes, they report that women who were “very satisfied” had a significantly lower median urgency incontinence index score after 10 years compared with those who were not “very satisfied” (0 vs 5, p<0.001). Similar results were found when comparing women stating that they were “cured” after 10 years compared with those stating not “cured” (0 vs 4.5, p<0.001). There are many additional longer term TVT studies, including; Liapis A, et al. Int Urogynecol J 2008; 19:1509–1512 (7 years follow up), Olsson I, et al. Int Urogynecol J Pelvic Floor Dysfunct 2010; 21:679–683 (11.5 years follow up), Groutz A, et al. Minim Invasive Gynecol 2011; 18:726–729 (10 years follow up), Aigmueller T, et al. Am J Obstet Gynecol. 2011; 205:496.e1-5 (10 years follow up), Heinonen P, et al. Int J Urol 2012; 19:1003–1009 (10.5 years follow up) and Serati M, et al. Eur Urol 2012; 61:939–946 (10 years follow up).

Nilsson reported the longest-term follow up after TVT in 2013 from the 3 center Nordic study (Nilsson 2013) with a 78% follow up rate. A stress test in the same manner as pre-operatively and during the 5, 7, and 11 years follow-up visits. Subjective success was assessed by the Patients Global Impression of improvement (PGII) and the following condition-specific Quality of Life (QoL) questionnaires: the IIQ-7, the UDI-6, the Urinary Incontinence Severity Score (UISS). The PGII included questions on if the women felt they were cured or if their incontinence had significantly improved or if they felt the incontinence was unchanged or worse. A visual analog scale (VAS) from 0 to 100, where 0 represented no urinary problems and 100 unbearable urinary symptoms, both pre-operatively and at the 17-year follow-up visit was also used. The women were asked if they experienced leakage on straining and if they would recommend the operation to a friend. Seventy-eight percent of the potentially assessable women were evaluated either by a clinic visit or by a telephone interview. One case of a minimal, symptom-free tape extrusion was seen. No other tape complications occurred. Over 90 % of the women were objectively continent. Eighty-seven per cent were subjectively cured or significantly improved. Most women with worsening leakage had a component of urgency incontinence.

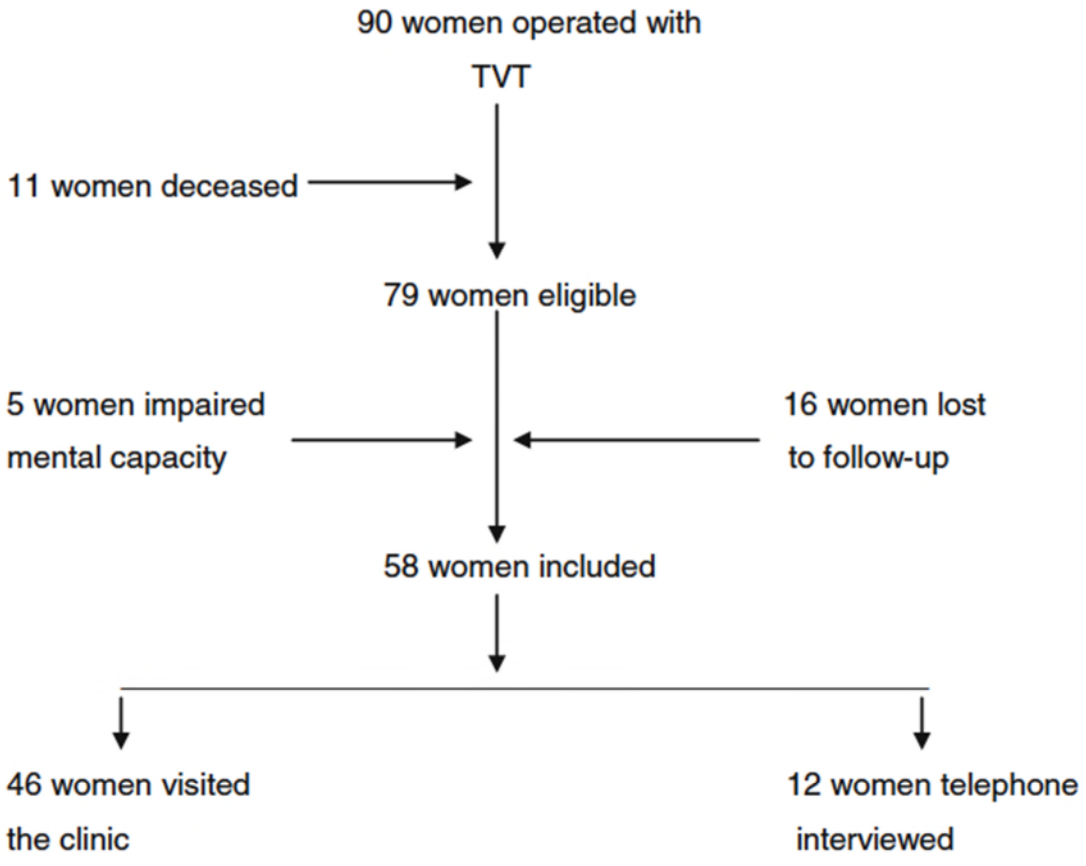

Fig. 1 Flow chart of the study

From Nilsson 2013)

Serati published a report on 63 women with at least 10-year follow up after TVT (Serati et al, EU, 2012). 58 patients were evaluable at 10 years (3 deceased and 2 lost to f/u), including physical examination. No woman required sling release, or experienced vaginal, bladder or urethral erosion or denovo dyspareunia. Denovo OAB symptoms were reported by 19/63 (30%) at 3 months, and 19% at 10 years. 17/19 women had DO on urodynamics. At 10 years, 89.7% of women were subjectively satisfied and 93.1 were objectively cured (no Sui on SUI test).

There are several TVT-O studies with longer term follow up. Cheng reported 103 women with TVT-O and minimum 5 year follow up. They noted 1 vaginal mesh exposure, and 4 patients with groin pain persisting to 1 year.

Laurikainen et al published a 5-year multicenter follow up of TVT and TVT-O with similar subjective success, 94.2 % TVT and 91.7% TVT-O, and combined objective subjective cure rates of > 80 % in each group. Physical exam was done and showed 1 vaginal mesh exposure at 1 year, with no additional vaginal, bladder or urethral mesh issues at the 5 year point (Laurikainen E, et al. Five-year Results of a Randomized Trial Comparing Retropubic and Transobturator Midurethral Slings for Stress Incontinence. Eur Urol (2014),)

Groutz published 5 year efficacy of TVT-O in 61 women including pelvic examination. She reports 74% cured, 8% improved and 18% failure. She reported 2 (3.2%), noted at one year, with no further mesh exposures noted at the 5 year point.

Athanasiou published the longest TVT-O outcomes to date, in 124 women with a median follow up of 90.3 months (range 80-103). Objective and subjective cure pats were 81.5 % and 83.5 % respectively. Physical examination was done and showed 1 (0.8%) woman with a midline vaginal mesh exposure noted at 1 year, no further mesh exposures were noted with follow up. Importantly, the quality of life outcomes measured by the KHQ showed statistically significant improvement in all domains at 7 years. They reported no persistent groin pain that they suggest this may be secondary to a minor modification of surgical technique.

I conclude from these studies that either RP or TO approach of MUS are very effective for treatment of SUI. The complications are few and can be managed. Importantly, patient satisfaction, arguably the most important outcome, is very high.

Complications

Complications associated with the TVT and TVT-O can be broadly placed in to three categories. Intraoperative, immediate post operative or long term post

operative. Intraoperative include adjacent organ injury (bladder, bowel, vascular, vaginal), early post operative complications include obstructed voiding, infection and pain, last post operative include urgency symptoms and mesh exposure / erosion.

Updated discussion of mesh exposure.

Mesh exposure is the only unique complication from using mesh to treat SUI. Every other issue, short term and chronic pain, wound infection, failure, obstruction, urgency, dyspareunia, suture erosion, urethral / bladder injury / erosion, and others can be observed with other SUI surgery. Small vaginal mesh exposures may heal with nonsurgical management such as topical estrogen. Larger exposures, if symptomatic, may be managed by secondary closure with or without excision of the exposed mesh.

Midurethral slings require less dissection than fascial pubovaginal sling
All MUS procedures, including retropubic (RP), transobturator (TO), or single-incision slings (SIS), are “tension-free”. They provide support under the hypermobile urethra only during times of increased abdominal pressure, leading to “dynamic kinking” of the urethra which prevents leakage of urine. The transvaginal tape (TVT) was the first midurethral sling, and it requires a less extensive dissection than the traditional fascial pubovaginal sling. The traditional pubovaginal sling dissection requires a wide vaginal incision and subsequent periurethral mobilization to permit passage of the surgeon’s finger (not just a narrow trocar) into the retropubic space. This allows for controlled guidance of the sling passage needle from the suprapubic incision onto the surgeon’s finger as it is passed behind the pubic bone and delivered through the vaginal incision. Precise control of the needle minimizes the chance of inadvertent bladder injury. In contrast, the TVT is a trocar-based device that places a piece of mesh tape retropubically through a limited vaginal incision and exits through a small suprapubic skin incision. The vaginal-to-suprapubic trocar passage is also called

the “bottom-up” approach. By 2001, the TO sling was developed. The TO sling follows a lateral vector, the natural curve of the vaginal wall, to pass the sling through the obturator fossa, which allows it to avoid the blind retropubic pass. With subsequent development of the “top-down” retropubic sling in 2001 and then the “inside-out” transobturator sling in 2003, four different methods of placing a MUS were available (RP: “bottom-up” and “top-down”; TO: “inside-out” and “outside-in”), each with its own benefits and complication profiles, secondary to their different vectors of passage. The SIS sling was FDA approved in 2006. It was designed to have the benefits of lateral vector passage, like a TO sling, but to avoid passage through the adductor muscle complex of the thigh, which is associated with rare pain complications.

Updated data on vaginal wall mesh exposure and mesh perforation in 2016 after MUS surgery, presented in this table.

	Retropubic	**Transobturator**	**Single-incision**
Vaginal wall mesh exposure	1.5%†	0.4%†	Higher than “inside-to-out” TO slings; RR 3.75, 95% CI 1.42 to 9.86‡
Bladder injury	2.7-3.9%†	0.4%†	0.8%§
Urethral injury	0.2-0.3%†	0.2-0.3%†	<4%‡
Bowel injury	0-0.04%†	0%†	0.8%§

†: Ford 2015

‡: Nambiar 2014

§: Barber 2012[6]

Mesh exposure reflects the RP and TO vectors of placement

Vector differences when passing the RP and TO sling trocars are directly related to the different rates and locations of vaginal wall mesh exposure. The increased incidence of mesh exposure with TO slings reflects the "smile" sling vector traveling from the midurethra, coursing laterally along the anterior vaginal wall, and passing towards the obturator foramen. At the lateral vaginal sulcus there is a potential for thinning of the vaginal wall, either due to individual patient anatomy or to surgeon dissection, and this may lead to mesh exposure. The RP sling has a "U" vector, which travels underneath the urethra, then directly behind the pubic bone. It does not travel laterally along the anterior vaginal wall. RP slings have a lower rate of mesh exposure than TO slings because passage of the RP sling avoids the lateral vaginal sulci (Deffieux 2010, Novara 2008). Mesh exposure after a RP sling most commonly occurs in the midline at the incision site.

Both RP and TO slings have 2 different entry points and trajectories: either from the vaginal incision to the outside skin ("bottom–up" RP sling and "inside-out" TO sling) or from the outside skin to the vaginal incision ("top-down" RP sling and "outside-in" TO sling). Because each courses laterally, both TO approaches still carry the risk of vaginal perforation at the lateral vaginal sulcus. In 341 women who underwent TO sling, Abdel-Fattah et al reported an increased risk of vaginal wall mesh exposure with the "outside-in" technique. Only 3 of 20 lateral sulcus injuries occurred after "inside-out" TO (TVT-O) slings versus 17 of 20 after "outside-in" TO slings ($p = 0.001$) (Abdel-Fattah 2010). Similar results were noted by But in 2008 (But 2008). The reason for the increased exposure rate with the "outside-in" approach may be due to the additional dissection required to allow a finger to receive the TO trocar at the pubic bone. It may also be secondary to the relative lack of three-dimensional orientation when receiving the sling trocar entering from the groin crease. This is in contrast with the "inside-out" technique, in which the surgeon places the trocar in a precise and controlled position under direct vision relative to the vaginal wall and urethra.

The single-incision sling, or “mini-sling”, follows the same vector as the TO sling, however, due to its shorter length, it only reaches to the obturator internus membrane. Because it has a similar lateral vector of passage along the anterior vaginal wall as the TO sling, SIS have a rate of mesh exposure of 1.3% (95% CI 0.8-1.9), comparable to the TO sling (Schimpf 2014).

In a 2014 meta-analysis, the rate of vaginal wall perforation by TO sling was 2.8% (95% CI 2.2-3.5%), whereas the rate of vaginal wall perforation by the RP sling was 0.73% (95% CI 0.40-1.2%) (Schimpf 2014). The Trial of Midurethral Slings (TOMUS), a high-quality multicenter RCT of 597 women, reported that the recognized vaginal wall trocar or perforation rate at the time of surgery was 4.4% with TO sling and 2% with RP sling, and the mesh exposure rates on follow-up were 1.3% with TO sling and 0.7% with RP sling (Richter 2010).

Clinical presentation of vaginal wall mesh exposure

Vaginal wall mesh exposure may be early or delayed and has a variety of presentations. A patient may be asymptomatic, with the sling visible or palpable only on physical examination. The symptomatic patient may have vaginal spotting or discharge, vaginal pain, dyspareunia and/or partner dyspareunia. Because symptoms can be non-specific, one must have a high index of suspicion with any post-operative sling patient.

Symptoms may begin within a few weeks to a few months after the procedure. Osborn et al. found that patients who had mesh exposure presented at a median of 6 months from the time of their initial surgery (Osborn 2014). The most common symptom was vaginal bleeding (20/50 women), reported as intermittent spotting increasing after intercourse. Vaginal discharge was reported in 3/50, 18/50 had dyspareunia, and 20/50 women had vaginal pain. Kokanali reported the most common presenting symptom of vaginal wall mesh exposure was the patient feeling the mesh on self-examination (Kokanali 2014). In the authors’

experience, when patients report vaginal pain or dyspareunia, we are also concerned that the sling may be too tight and are careful to evaluate for evidence of pelvic floor muscle dysfunction / spasm.

According to a 2013 review of 188,454 index patients who underwent midurethral sling placement, the risk of surgical removal or revision due to mesh exposure increases throughout the first four years after surgery, from 1.3% at 1 year to 2.1% at four years post-operatively. After that time, the rate of surgical intervention for mesh exposure remains around 2.5% (Jonsson 2013). These findings are consistent with the 5-year results from the Trial of Midurethral Slings (TOMUS), which reported a 1.7% rate of mesh exposure (Kenton 2015).

The RP MUS has been extensively studied, with average follow-up greater than 10 years in several publications. These studies inform the clinician that there is a continued, but small, risk for vaginal mesh exposure. In the Nordic study, only one of 46 women who did not have mesh exposure at 7 years and returned for the seventeen-year physical examination had mesh exposure (Nilsson 2013). Similarly, Svenningsen reported 0.6% mesh exposure rate at mean follow-up of almost 11 years (Svenningsen 2014). The longest published TO sling follow-up study reported 2/61 women had vaginal mesh exposure at 5 years, and, importantly, both were recognized on the 1 year exam (Groutz 2011).

Adjacent Organ Perforation

Bladder injury is higher with the RP sling

Bladder perforation is more common with RP slings due to the blind pass and trajectory of the retropubic trocar behind the pubic bone. Most current literature describes bladder trocar injury at the time of the index surgery. A 2015 meta-analysis reported a 3.2% rate of bladder perforation with RP sling, significantly higher than the TO sling rate of 0.2% (OR 5.72, CI 2.94-11.12, $p < 0.0001$) (Seklehner 2015). The TOMUS trial, which consisted of high volume fellowship-

trained surgeons practicing at teaching institutions, reported a 5% rate of bladder perforation and 1% urethral perforation rate with the RP sling compared to 0% bladder and 0% urethral perforation with the TO sling (Richter 2010). The rate of bladder or urethral trocar injury with TO surgery in other randomized studies is reported between 0 and 1.3% 9(Richter 2010, Porena 2007). Interestingly, Tamussino reported 9/10 bladder injuries occurred with the "outside-in" TO trocar technique (Tamussino 2007).

Several risk factors are associated with bladder perforation. First, as with any procedure, there is a learning curve, so proper training and surgeon experience are important. Stav et al. reported that 32/34 (94%) bladder perforations were by surgeons who had performed fewer than 50 slings ($p < 0.0001$). All but one of these perforations was by a RP sling, and the route of trocar insertion ("top-down" or "bottom-up") did not affect risk (Stav 2009). History of prior abdominal or pelvic surgery that may scar the retropubic space can increase the risk of bladder perforation, including colposuspension, cesarean section, or prior anti-incontinence surgery. Diabetes mellitus is a medical comorbidity that may increase the risk of bladder perforation. Chen noted an increased risk of mesh perforation into the bladder in diabetic patients, possibly related to their poor wound healing abilities (Chen 2008). Interestingly several series have reported decreased rates of bladder perforations with RP slings in patients with BMI > 30 kg/m^2 (Stav 2009, Bohlin 2015, Lovatsis 2003). The protective mechanism may be that the retropubic fat pushes the bladder away from the pubic bone, shielding the bladder from the trocar.

Urethral injury is less common but can be more complex

Urethral injuries are uncommon, occurring in 0.2-0.3% of MUS surgeries (Stav 2009, Clemons 2013). The urethra can be injured during dissection or trocar placement, or delayed mesh perforation can occur secondary to technical factors or tissue characteristics. Patient factors that increase the risk of urethral perforation include previous surgery with scarring, any condition causing poor

vascularity, including a history of radiation, estrogen deficiency or urethral atrophy. Technical factors predisposing to delayed urethral perforation include over tensioning of the sling, dissecting too deeply into the urethral wall, of placement of the sling trocar partially through the urethral wall at the time of surgery. Importantly, urethral dilation post-operatively to loosen an obstructive sling is not only ineffective at relieving obstruction but has also been reported to cause urethral perforation[7].

Sling perforation of the bowel

Bowel injury during midurethral sling placement is exceedingly rare, reported in 0-0.04% of cases (Kenton 2015, Meschia 2002, Tamussion 2001). All reported bowel injuries have occurred after the RP sling, which is intuitive, considering that the TO sling avoids the pelvic compartment. Typically, bowel injuries occur in patients with a history of prior abdominal or pelvic surgery and adhesions of the bowel to the pelvis. Most commonly the patient presents within hours to several days after surgery with abdominal pain, nausea, vomiting, decreased urine output, other signs of peritonitis, and possibly passage of bowel contents through the suprapubic trocar sites. However, patients can have significantly delayed and atypical presentations. Some patients may not have signs or symptoms of peritonitis at presentation (de Aleida 2013), and Elliott reported an asymptomatic patient whose bowel injury was found incidentally (Elliott 2012). Chelvaratnam and Phillips both describe patients who presented years after their RP sling. One report describes a patient with symptoms of diarrhea and right-sided abdominal pain who was found to have the RP sling perforated into the ascending colon (Chelvaratnam 2015, Phillips 2009). Another patient presented with a de novo small bowel obstruction whose laparotomy showed that the sling had penetrated the peritoneum and caused inflammation near the terminal ileum, leading to local adhesions and bowel obstruction[63]. Bowel injury in the patient with peritoneal signs may be confirmed with free infra-diaphragmatic air on plain abdominal x-ray. In a patient with a less clear or more insidious clinical course, CT scan of the abdomen and pelvis is appropriate.

To prevent potential bowel injury, de Almeida recommend preoperative CT in high-risk patients to permit localization of the bowel and to evaluate for any pelvic adhesions, or one can choose to place a TO instead to avoid the pelvis and any bowel injury (de Almeida 2013). Overall the risk of bowel injury remains low but is an important consideration when choosing which sling procedure to perform in a given patient.

Pain

The 2015 Cochrane report shows that there was a significantly higher occurrence of groin pain in women who underwent a TOR procedure than in women who underwent a RPR procedure (RR 4.12, 95% CI 2.71 to 6.27; Analysis 1.24). The average rate of groin pain across both groups was 4.51% and, using this as the assumed control rate in the RPR group, therewere 163 more cases per 1000 in the TOR group (95% CI from 94 to 266 per 1000 more). Conversely, suprapubic pain was found to be significantly lower in women who underwent a TOR procedure than a RPR procedure (RR 0.29, 95% CI 0.11 to 0.78; Analysis 1.25). Both groin and suprapubic pain occurrence were short-lasting, with most resolving within the first six months. The duration of pain ranged from two to 52 weeks, with a median duration of eight weeks.

Finally, one must put a reported “complication” in a published manuscript in context with the patient symptoms. What surgeons report as an adverse event may not be clinically significant. In addition, where media attention has emphasized issues like mesh exposure as a major event, the experienced clinician recognizes that mesh exposure has much less negative clinical impact than bladder obstruction or post operative urgency symptoms. This is why the Cochrane review summarizes the data the way they do, with results, followed by obstruction and urgency symptoms, then with procedure specific complications. These are the most relevant clinical decision makers for surgeons. The 2011 Cochrane review on Minimally invasive slings reports:

"Sixty-two trials involving 7,101 women were included. The quality of evidence was moderate for most trials. Minimally invasive synthetic suburethral sling operations appeared to be as effective as traditional suburethral slings [8 trials, n=599, risk ratio (RR) 1.03, 95% confidence interval (CI) 0.94--1.13] but with shorter operating
time and less postoperative voiding dysfunction and de novo urgency symptoms. Minimally invasive synthetic suburethral sling operations appeared to be as effective as open retropubic colposuspension (subjective cure rate at 12 months RR 0.96, 95% CI: 0.90--1.03; at 5 years RR 0.91, 95% CI: 0.74--1.12) with fewer perioperative complications, less postoperative voiding dysfunction, shorter operative time, and hospital stay but significantly more bladder perforations (6% vs. 1%, RR 4.24, 95% CI: 1.71--10.52). There was conflicting evidence about the effectiveness of minimally invasive synthetic suburethral sling operations compared to laparoscopic colposuspension in the short term (objective cure, RR 1.15, 95% CI: 1.06--1.24; subjective cure RR 1.11, 95% CI: 0.99--1.24). Minimally invasive synthetic suburethral sling operations had significantly less de novo urgency and urgency incontinence, shorter operating time, hospital stay, and time to return to daily activities. A retropubic bottom-to-top route was more effective than top-to bottom route (RR 1.10, 95% CI: 1.01--1.20; RR 1.06, 95% CI: 1.01--1.11) and incurred significantly less voiding dysfunction, bladder perforations, and tape erosions. Monofilament tapes had significantly higher objective cure rates (RR 1.15, 95% CI: 1.02--1.30) compared to multifilament tapes and fewer tape erosions (1.3% vs. 6% RR 0.25, 95% CI: 0.06--1.00). The obturator route was less favorable than the retropubic route in objective cure (84% vs. 88%; RR 0.96, 95% CI: 0.93--0.99; 17 trials, n=2,434), although there was no difference in subjective cure rates. However, there was less voiding dysfunction, blood loss, bladder perforation (0.3% vs. 5.5%, RR 0.14, 95% CI: 0.07--0.26), and shorter operating time with the obturator route.

Persistent pain in the groin or thigh occurs more commonly with the transobturator approach than retropubic surgery. Laurikainen *et al.* reported that 16% of women randomized to undergo insertion of an inside-out transobturator sling experienced groin pain compared with only 1.5% of those in the TVT™ arm. Similarly, Wang and colleagues reported pain in 8.2% of patients after TVT-O™ compared with only 2.6% of those who underwent TVT™ insertion. In meta-analyses, Long *et al.* and Latthe *et al.* confirmed that groin or thigh pain was reported more frequently after transobturator insertion than retropubic procedures. Duckett (*BJU Int.* 95, 95–97 (2005) reviewed different strategies for managing groin pain after retropubic midurethral slings including initial conservative management with the use of nonsteroidal anti-inflammatory agents, injection of corticosteroids and local anaesthetic, and even mesh excision. This pain usually goes away within weeks.

Gruber reported the TO sling traveling through the obturator foramen could be safely removed through a combined vaginal and transcutaneous approach (Gruber 2011).

Seratti reported evaluate the efficacy and safety of TVT-O 5-yr implantation for management of pure SUI in 191 women. Nineteen (9.9%) patients complained of groin pain 24 h after surgery. One month after surgery, six (3.1%) women complained of groin pain and this symptom remained in two (1.0%) even 1 yr after surgery (p for trend <0.0001). At 5-yr follow-up, no cases of groin pain remained.

Quality of life / overall patient satisfaction are affected not only by the outcome of the incontinence surgery from the standpoint of cure or improvement but also by the appearance of voiding difficulties, urgency symptoms, UTIs, or other adverse consequences of the surgical procedure itself. The evidence suggests that a minimally invasive procedure that is standardized can decrease rates of complications. The Finnish TVT registry demonstrated a learning curve for surgeons adopting the TVT (Kuuva and Nilsson, 2003). This registry is unique in

that all TVT procedures are recorded and the data reflect the entire national experience with a new procedure. Overall, the rate of complications associated with the TVT procedure is relatively low. Bladder injury in the two national registries ranges from 2.7% to 3.8%. Voiding dysfunction is reported as approximately 7.6%, and wound healing problems are less than 1%.

The TOMUS study, the landmark NIH sponsored multicenter prospective randomized trial of 597 women carefully recorded and reported complications of the RP and TO midurethral sling procedures, presented 12 month data in Table 2 below (Richter 2010).

Table 2. Adverse Events, According to Treatment Group, Severity, and System.*

Adverse Event	Retropubic Sling (N=298)		Transobturator Sling (N=299)		P Value
	Events	Patients	Events	Patients	
	no.	*no. (%)*	*no.*	*no. (%)*	
Serious adverse event	43	41 (13.8)	20	19 (6.4)	0.003
Wound-related event	10	9 (3.0)	5	5 (1.7)	0.30
Mesh exposure†	9	8 (2.7)	1	1 (0.3)	
Mesh erosion‡	1	1 (0.3)	1	1 (0.3)	
Surgical-site infection	0	0	2	2 (0.7)	
Granulation tissue	0	0	1	1 (0.3)	
Genitourinary event	23	23 (7.7)	13	13 (4.3)	0.09
Urethral perforation	1	1 (0.3)	0	0	
Bladder perforation§	15	15 (5.0)	0	0	
Vaginal epithelial perforation	6	6 (2.0)	13	13 (4.3)	
Recurrent cystitis, leading to diagnostic cystoscopy¶	1	1 (0.3)	0	0	
Vascular or hematologic event	1	1 (0.3)	1	1 (0.3)	>0.99
Pulmonary embolus	0	0	1	1 (0.3)	
Postoperative bleeding	1	1 (0.3)	0	0	
Neurologic symptoms‖	1	1 (0.3)	0	0	0.50
Voiding dysfunction requiring surgery, use of catheter, or both	9	8 (2.7)	0	0	0.004
Other (urothelial abrasion)	0	0	1	1 (0.3)	0.50

TOMUS is important because there were 43 surgeons from 9 clinical centers that participated, making the findings generalizable. The critical findings were that

bladder perforations from trocar passage and voiding dysfunction requiring surgical intervention were uncommon but occurred only in women who received the RP sling; women in this group were also more likely than women in the TO-sling group to have a higher (100 ml or more) residual volume after voiding at the time of discharge from the hospital (P = 0.02) and to have postoperative urinary tract infections (P = 0.04). More vaginal perforations occurred in the TO- sling group than in the RP- sling group (13 vs. 6); the majority of those in the TO-sling group occurred when the in-to-out approach was used (10). The frequency of neurologic symptoms was also higher in the TO-sling group than in the RP-sling group (P = 0.01); weakness in the upper leg was the most common neurologic symptom, occurring in 24 (60%) of those who reported neurologic symptoms.

TOMUS 24 month follow up adverse event data was published by Brubaker et al (2012). The table presents the AE's from TOMUS. A total of 383 adverse events were observed among 253 of the 597 women (42%). Seventy-five adverse events (20%) were classified as serious (serious adverse events); occurring in 70 women. Intraoperative bladder perforation (15 events) occurred exclusively in the retropubic group. Neurologic adverse events were more common in the transobturator group than in retropubic (32 events vs 20 events, respectively). Twenty-three (4%) women experienced mesh complications, including delayed presentations, in both groups.

The methods of reporting pain and other local complications after TO and RP sling were particulary good in the TOMUS trial. Participants were asked to identify specific locations of pain, using anatomic pictures, and rate the intensity of the pain associated with the study surgery. Patient self-reports were collected daily for the first 2 weeks after surgery, then at each subsequent study visit. Patients who reported surgical pain at the 2-week follow-up visit were asked to complete a daily pain diary for an additional 2 weeks. Neurologic symptoms were defined as new paresthesias or alterations in motor function that developed within the first 6 weeks after surgery. Participants were considered to have a

neurologic complication related to TOMUS surgery if the patient responded affirmatively to either of the following questions; “do you have any numbness in your legs or pelvic area that has developed since surgery?” and “do you have any weakness in your legs or pelvic area that has developed since surgery?” Patients who responded affirmatively were asked to specify the location and magnitude of the symptoms. They were also asked about bother with response categories of “not at all, slightly, moderately or greatly bothersome.”

TABLE 1
Complications by treatment group at 24 months

Variable	No. of events/No. patients (% complication rate) Retropubic	Transobturator	*P* value*
Total no. of patients	298	299	
SAEs			
Bladder perforation	15/15 (5.0%)	0/0	< .0001
Urethral perforation	1/1 (0.3%)	0/0	.50
Pulmonary embolus	0/0	1/1 (0.3%)	> .99
Postoperative bleeding	1/1 (0.3%)	0/0	.50
Mesh complication: erosion	1/1 (0.3%)	1/1 (0.3%)	> .99
Mesh complication: exposure	10/9 (3.0%)	6/6 (2.0%)	.45
Surg site inf: deep incisional	0/0	1/1 (0.3%)	> .99
Surg site inf: organ/space	0/0	2/2 (0.7%)	.50
Recurrent UTI	3/3 (1.0%)	0/0	.12
Neurologic symptoms	1/1 (0.3%)	0/0	.50
Granulation tissue	0/0	1/1 (0.3%)	> .99
Vaginal epithelium perforation	6/6 (2.0%)	13/13 (4.4%)	.16
Voiding dysfunction requiring surgery (and/or catheter use)	9/9 (3.0%)	0/0	.002
Other	0/0	3/3 (1.0%)	.25
Total SAEs	47/45 (15.1%)	28/25 (8.4%)	.01
AEs			
Intraoperative bleeding	14/14 (4.7%)	7/7 (2.3%)	.13
Postoperative bleeding	6/6 (2.0%)	0/0	.02
Mesh complication: exposure	4/4 (1.3%)	2/2 (0.7%)	.45
Surg site inf: superficial incisional	2/2 (0.7%)	0/0	.25
UTI culture proven	27/25 (8.4%)	16/14 (4.7%)	.07
Empiric	16/15 (5.0%)	9/9 (3.0%)	.22
Recurrent	18/16 (5.4%)	10/10 (3.4%)	.24
Neurologic symptoms	20/15 (5.0%)	32/29 (9.7%)	.04
Voiding dysfunction	10/10 (3.4%)	6/6 (2.0%)	.33
Pain per patient self-report ≥6 wk	7/7 (2.3%)	7/6 (2.0%)	.79
De novo urge incontinence	0/0	1/1 (0.3%)	> .99
Persistent urge incontinence	42/42 (14.1%)	38/38 (12.8%)	.63
Other	8/7 (2.3%)	6/6 (2.0%)	.79
Total AEs	174/121 (40.6%)	134/98 (32.8%)	.051

AE, adverse event; *SAE*, serious adverse event; *UTI*, urinary tract infection.

* *P* values were from Fisher exact test comparing the rate.

Brubaker. Complications of midurethral slings. Am J Obstet Gynecol 2011.

Assessment of clinically important AEs in surgical trials remains a challenge. AE definitions and reporting vary between investigators making it difficult to compare data from one study to the next. Standardization of event classification with a surgical complication scale (such as Dindo) is a good first start; however, the instrument was not developed for assessment of the complications profile typical for midurethral slings. Moreover, these scales do not take into account the patient perception of complications that may differ from the physician perspective. We found that although the Dindo scale allowed us to reliably define and capture events across multiple investigators and clinical sites, at times the events were allocated to categories that were not compatible with the patient's clinical course; for example, a perforation of the bladder during retropubic sling requires a simple replacement of the sling needles, but is categorized as an SAE because in the Dindo classification, any additional procedures, however small, are categorized as "severe." Although bladder or vaginal perforations are undesirable events, we did not detect clinically relevant consequences in a 2-year follow-up.

In the first 2 years after midurethral sling surgery, 42% of women undergoing TOMUS midurethral sling procedures experienced at least 1 AE. These numbers are less than those observed in the SISTEr trial after fascial pubovaginal sing group 63%, (415 events among 206 women) and are similar to the Burch group, 47% (305 events among 156 women) (Albo, 2007). Most of these complications occurred during surgery or within the first 6 weeks after surgery. Complication patterns differed by surgical approach, with bladder perforation, voiding dysfunction requiring surgical treatment and UTI occurring more commonly in the retropubic group and neurologic symptoms occurring more commonly in the transobturator group. Because surgical efficacy is similar for these 2 procedures, the differences in type and frequency of AEs may influence the decision on which type of surgery is to be performed. Postoperative mesh complications occurred in both groups with new problems occurring in the second postoperative year in a minority of women. UTI was the most common AE in both surgical groups. Most

events occurred within the first 6 weeks after surgery. The higher incidence of UTIs in the retropubic group may be related to the higher rate of voiding dysfunction. Data from both the SISTEr and TOMUS trials demonstrate a high incidence of UTI after surgery for stress incontinence.

The number of mesh complications was similar to what has been reported elsewhere. Most are vaginal exposures that did not require surgical treatment. Mesh-related complications continued to occur up to 2 years after surgery, however, events were infrequent. During months 12-24, there were 3 new mesh-related SAEs. This data is unique in that the TOMUS SAE and AE data were collected prospectively and robustly as part of a large, randomized surgical trial. Quality controls included a predefined list of AEs to monitor. Cross-checks of related variables on study forms were performed at every visit and patients were also queried about office visits outside of their follow- up time points. Furthermore, a complications work group reviewed, categorized and graded all complications in blinded fashion using a validated surgical complication instrument.

There were three European registries on the standard TVT procedure. Outcome from an Austrian registry involving 2,795 women and 55 gynecology units has been reported. A bladder perforation rate of 2.7% was reported and 68 patients (2.4%) patients required reoperation including 19 for hematoma (0.7%) [Tamussino KF, Hanzal E, Kölle D, Ralph G, Riss PA, Austrian Urogynecology Working Group (2001) Tension-free vaginal tape operation: results of the Austrian registry. Obstet Gynecol 98 (5 Pt 1):732–736]. In a registry from The Netherlands involving 809 women, a hematoma rate of 3.4% was reported [Schraffordt Koops SE, Bisseling TM, Heintz AP, Vervest HA (2006) The effectiveness of tension-free vaginal tape (TVT) and quality of life measured in women with previous urogynecologic surgery: analysis from The Netherlands TVT database. Am J Obstet Gynecol 195(2):439–444]. In a Finnish registry of 1,455 TVT procedures conducted by the end of 1999, the rate of retropubic hematoma was 1.9% (Kuuva N, Nilsson CG (2002) A nationwide analysis of

complications associated with the tension-free vaginal tape (TVT) procedure. Acta Obstet Gynecol Scand 81(1):72–77.]

The Cochrane Review from 2011 (Ogah) “reviews major complications such as nerve, bowel or major vascular injuries, pelvic hematoma, necrotizing fasciitis, ischiorectal abscess, and death are uncommon and unlikely to be picked up by small RCTs. The true incidence is more likely to be determined from large national registries and voluntary reporting registries or databases for reporting complications, such as the FDA’s manufacturer and user facility device experience (MAUDE). Several of these registries have reported on TVT.70--72 The number of procedures ranged from 809 to 2,795, and the rate of major complications was low: bladder perforation occurred in 2.7--3.9% of cases (significantly higher in those with previous pelvic organ prolapse or incontinence surgery). There was no record of the sequelae of the perforations. Reoperation rates relating to tape insertion or postoperative voiding dysfunction ranged from 1.6% to 2.4%; pelvic hematoma occurred in 0.7--1.9% of women, the majority of which needed no intervention, and only one case of bowel injury was recorded. Registries of Transobturator Tapes reported much lower rates of complications (e.g., bladder perforation in 0.4%).73,74 Reoperation occurred in 0.8--2.2% of women and hematoma occurred in 1 out of 2,543 procedures. Urethral injury rates ranged from 0.08% to 0.1%. It is noteworthy that many of the trials included in our review did not report rates of urethral injuries. This is a rare complication but has significant morbidity and is likely to be under-reported”.

A 2015 Cochrane Review update on MUS reported major vascular injury such as retropubic hematoma or major visceral injury, for example bowel perforation, was reported by 28 trials with 4676 women. This occurred significantly less often with TO than with RP sling (RR 0.33, 95% CI 0.19 to 0.55; Analysis 1.15). Also, that bladder/urethral perforation was reported by forty trials and the rate was significantly lower in the TOR group than the RPR group (RR 0.13, 95% CI 0.08 to 0.20; Analysis 1.16). The average bladder perforation rate across both groups

was 2.54% and, using this as the assumed control bladder perforation rate in the RPR group, there were 22 fewer perforations per 1000 in the TOR group (95% CI from 20 to 23 per 1000 fewer).

Schimpf in 2014 reported a meta-analysis of the literature comparing MUS, fascial sling and Burch BNS. Adverse event and perioperative outcome data were highly variable by each outcome and did not provide a consistent direction when examined by absolute rates of complications for each surgery (Appendix, Table 3). Retropubic slings result in lower absolute rates of sling erosion, need to return to the OR for treatment of sling erosion, nerve injury, ureteral injury, groin/leg pain, and vaginal perforation. Obturator MUS result in shorter operative time, lower blood loss, fewer bladder/urethral perforations, less perioperative pain, fewer UTIs, and less overactive bladder symptoms. Meta-analysis showed that postoperative overactive bladder symptoms were more common in patients following retropubic slings (OR 1.413, CI 1.01-1.98, p=0.046). There was no difference between slings on meta-analysis of return for OR for erosion or for retention. There were too few studies that examined subpopulations of stress-incontinent patients (e.g. those with intrinsic sphincter deficiency or prior surgical failures) to allow meta-analysis.

In summary, for women considering a retropubic or transobturator MUS, they recommend either intervention for objective and subjective cure; the decision should be based on surgeon expertise accounting for adverse events (Schimpf 2014).

Importance of Pelvic Floor Dysfunction and Chronic Pain Syndromes

Pelvic floor muscle dysfunction

In my opinion, one of the most critical advances in our knowledge to help manage pelvic pain is the identification of pelvic floor muscle dysfunction. The pelvic floor muscles are under stress with our physical activities, and in some

men and women, the muscles become tense, spasm, “cramp”, and this causes pain. Most people cannot identify that they are having pelvic floor muscle spasms or cramps. Instead, they can describe several different types of pain or other symptoms including pain in the pelvis, pain with sitting, pain “in the bladder” or pain with sex. When the pelvic floor muscles are dysfunctional any of the three organs that go through the pelvic floor, the urethra, rectum and /or the vagina can be affected.

Pelvic floor muscle dysfunction means that the pelvic floor muscles are too tight and need to relax. This is a primary musculoskeletal problem with the levator ani muscles. When men and women have pelvic floor dysfunction, they may have urinary symptoms from the muscles squeezing inappropriately against the urethra. An important symptom we use clinically to help us identify pelvic floor dysfunction is pain with sex. The role of pelvic floor dysfunction as a cause of pain during sex pain, as well as daily pelvic pain, has become increasingly accepted, although the prevalence remains unknown [Messelink B, Benson T, Berghmans B, et al. Standardization of terminology of pelvic floor muscle function and dysfunction: report from the pelvic floor clinical assessment group of the International Continence Society. Neurourol Urodyn. 2005;24:374–380, Latthe P, Mignini L, Gray R, Hills R, Khan K. Factors predisposing women to chronic pelvic pain: systematic review. Br Med J. 2006; 332:749–755.]. The levator ani complex is composed of 2 distinct muscles, the iliococcygeus and pubococcygeus muscles, and dysfunction occurs through persistent contraction or inability to completely relax the muscle complex. Hypertonicity of the levator ani may result in either introital or deep dyspareunia. Women may report a history of prolonged discomfort for several hours or days after an episode of intercourse.

Clinicians were slow to recognize that many patients with pelvic pain and bladder symptoms had pelvic floor muscle dysfunction. Many of these papers I will discuss are reporting on patients with presumed diagnosis of Interstitial Cystitis (IC) and this literature really helped us understand pelvic floor dysfunction.

Weiss reported success in treating IC with pelvic floor with physical therapy (Weiss JM. Pelvic floor myofascial trigger points: manual therapy for interstitial cystitis and the urgency–frequency syndrome. J Urol. 2001;166:2226–31.) Christine Whitmore co-authored an abstract in 2001 that discusses pelvic floor PT, reporting that in 16 women with the diagnosis of IC or pelvic floor dysfunction treated with physical therapy there was a 94% improvement in dyspareunia rate and 9/16 resumed pain free sex. They conclude that PT was most effective in women with urinary frequency, supra pubic pain and pain with sex. (ICBR-51 The Effect of Manual Physical Therapy in Patients Diagnosed with Interstitial Cystitis, High-Tone Pelvic Floor Dysfunction, and Sacroiliac Dysfunction J. Lukban, K. Whitmore, S. Kellogg-Spadt, R. Bologna, A. Lesher, and E. Fletcher). Peters, in 2007, showed that in 75 women referred for IC symptoms, 87% had pain with palpation of the pelvic floor muscles. Srinivasan et al., also in 2007, reported on pelvic floor PT and injections to treat myofascial pain.

By 2009 Butrick published a report focusing on pelvic floor dysfunction that explains in detail pelvic floor muscle hypertonicity. “Any pelvic pain disorder that is prolonged or particularly intense can result in such a barrage of noxious stimuli to the dorsal horn that it could result in upregulation of the dorsal horn. This results in neuropathic changes that involve a decrease in the sensory threshold of afferent nerves that leads to the finding of allodynia (stimuli that would normally not be painful are perceived as painful).”

As clinicians, we slow to understand pelvic floor dysfunction, wind up, and how it affects our patients and their outcomes with the surgeries we perform. It was in 2012 that Fitzgerald and others completed an NIH prospective, randomized, multicenter trial reporting that a significantly larger number of women with Interstitial Cystitis/ Painful bladder syndrome responded to pelvic floor muscle physical therapy than the control group. This was an important well done study that identified physical therapy of the pelvic floor muscles as an effective

treatment for these patients. The fact that this was published in 2012 reinforces how long it took for this thought process to gain traction. A 2015 NIH funded study found that pelvic muscle physical therapy improved the symptoms of both men and women with chronic pelvic pain syndromes (Appl Psychophysiol Biofeedback, Anderson et al, Feb, 2015). This understanding of pelvic floor dysfunction as a source of pain is more common in 2015, but surprisingly has still not been adopted by everyone. We talk about the pelvic floor commonly in our conferences, and many of us are surprised that some centers still do not evaluate the pelvic floor muscles, preferring treat the pelvic pain, particularly in patients who have had mesh placed (sling or prolapse) with surgery first.

In 2010, Dr. Butrick wrote. " I contend that it is not the mesh kit but the patient selection that is the key to preventing the induction of chronic myofascial pain and at times causing these patients to become a pelvic cripple; unable to stand, sit, or have intercourse. Therefore, do guns kill people? No, people kill people….." Butrick, C. Int Urogynecol J (2010) 21:133-134

To illustrate how complicated pelvic pain can be, I reproduce two tables from Dr. Butrick's 2009 paper. Table 1 lists causes of pelvic pain, table 2 the symptoms of pelvic floor muscle dysfunction.

Table 1. Causes of chronic pelvic pain
Urologic
Interstitial cystitis
Radiation cystitis
Urolithiasis
Recurrent urinary tract infection
Urethritis
Detrusor-sphincter dyssynergia
Prostatodynia
Chronic prostatitis type III
Chronic orchalgia
Gastrointestinal
Inflammatory bowel disease
Irritable bowel syndrome
Colon cancer
Diverticular disease
Chronic constipation
Colitis
Hemorrhoids
Female reproductive
Endometriosis
Pelvic inflammatory disease
Adhesions
Tuberculous salpingitis
Pelvic congestion syndrome
Ovarian cysts
Leiomyoma in uterus
Genital organ prolapse
Intrauterine devices
Musculoskeletal and neurologic disorders
Abdominal wall myofascial pain
Fibromyalgia
Poor posture
Pelvic floor myalgia
Piriformis syndrome
Nerve entrapment
Spinal cord/nerve root impingement secondary to vertebral column/retroperitoneal pathology
Herpes-zoster
Psychologic
Depression
Personality disorders
Sleep disorders
Physical or sexual abuse

Table 2. Common symptoms of pelvic floor dysfunction
Urologic
Daytime urinary frequency
Sensation of incomplete voiding
Urinary hesitancy
Varied force of urinary stream
Discomfort with bladder filling
Pain with ejaculation
Gynecologic
Deep dyspareunia
Increased pelvic discomfort "day after" sexual intercourse
Colorectal
Chronic constipation
Increased pain or discomfort shortly after defecation
Sensation of "sitting on golf ball"
Miscellaneous
Lower back pain
Pain referred to inner thighs

A critical issue is that when mesh is used we are taught to be careful with how we place the mesh, the amount of tension we place on the repair, the anchoring bands as they insert into the ligaments and/ or travel through the pelvic floor muscles. We observe that if the repair is too tight, there can be pain and pain with sex. We know that if we place sutures for a native tissue vaginal repair, and make a "shelf" or make the levators too tight, we can cause pain and pain with sex. We know that some of these women develop pelvic floor muscle dysfunction and pain from either the sutures or mesh placed under too much tension. We know that when we identify a tight band, and cut the tight band, releasing the tension, the pain can improve.

It is my opinion that many women with pelvic pain after vaginal surgery have pelvic floor muscle dysfunction and can be treated with pelvic muscle directed treatments, and do not need surgery for mesh removal. There are a few surgeons nationally who advertise themselves as specialists in mesh removal, some of them work closely with attorneys, and they tell patients that they need

surgery to remove mesh. These surgeons do not evaluate or treat the pelvic floor muscles first. The psychological impact on patients is worsened by years of aggressive TV advertising and phone calls telling patients that mesh is a problem and that the mesh needs to be removed. Many patients have come into my office with no symptoms or complaints, are doing very well, and tell me that they want their mesh removed. Some of them do not even have mesh.

I observe debates at our national meetings when some centers will present data on patient pain resolution vs. no resolution after mesh removal. When challenged these surgeons admit they do not evaluate the patient's pelvic floor muscles to check for pelvic floor dysfunction before surgery. Audience members then discuss that they see this exact type of pain in women who have never had surgery, or have had surgery but do not have mesh. They evaluate and identify pelvic floor dysfunction, most (my opinion, we are studying this rate now) of the patients improve with physical therapy, and do not need surgery.

Media driven hysteria about mesh placement and the need for removal is such a problem, so many patients are calling concerned that their sling that has been doing well for years needs to be removed, that the AUA published in June 2015 *Choosing Wisely* (www. choosingwisely.org)

The AUA reiterates its recommendation

"Don't remove synthetic vaginal mesh in asymptomatic patients.

"There is no clear benefit to mesh removal in the absence of symptoms, and mesh removal in this circumstance exposes the patient to potential complications.."

Chronic Pain Syndromes

Our literature has developed more in recent years to describe this complicated population, their evaluation and surgical outcomes. I again use Interstitial

Cystitis as a mechanism to discuss pelvic pain, since there is a lot of literature specifically on these patients that also help characterize the chronic pelvic pain patient. There were few studies that were published to investigate the association of different symptoms in these patients. Clauw et al described the association of IC with fibromyalgia as early as 1997, and suggested that the symptom overlap suggest IC patients have a more complicated pain threshold with centrally mediated pain in addition to peripheral pain (Clauw et al, J psych res 31: (1) 125-131, 1997).

Erickson showed that patients with interstitial cystitis had higher scores than controls for 2 reference symptoms, including other pelvic discomfort, backache, dizziness, chest pain, aches in joints, abdominal cramps, nausea, heart pounding and headache ($p < 0.01$) (Erickson et al. J Urol Vol. 166, 557–562, August 2001).

Clemens in 2008 looked at physician assigned diagnoses in an electronic medical record to assess comorbidities associated with interstitial cystitis. They report that *this was the first population based analysis of medical comorbidities associated with IC/PBS*. Their report on 239 women with IC, 239 of them matched with 717 controls (3:1 ratio). The found 23 diagnoses that were most commonly diagnosed with IC, $p < 0.005$ (Clemens et al, Case-Control Study of Medical Comorbidities in Women With Interstitial Cystitis. J Urol Vol. 179, 2222-2225, June 2008). The table below lists the co-morbidities associated with IC, note how many different symptom complexes are associated, many of them vague.

Diagnoses associated with IC

Diagnosis (ICD-9)	% Cases	% Controls	p Value	OR
Overall No.	239	717		
Other disorders of bladder (596)	12.1	0.7	<0.00001	19.7
Other disorders of urethra + urinary tract (599)	14.6	1.0	<0.00001	17.4
Drug dependence (304)	2.1	0.1	0.0009	15.3
Gastritis + duodenitis (535)	1.7	0.1	0.004	12.2
Endometriosis (617)	4.2	0.4	0.00001	10.4
Late effects of other + unspecified external causes (909):	3.8	0.4	0.00006	9.3
Late effect of child abuse (909.9A)	3.8	0.4	0.00006	9.3
Other disorders of intestine (569)	3.3	0.4	0.0002	8.2
Symptoms involving urinary system (788)	15.5	2.8	<0.00001	6.4
Disorders of function of stomach (536)	6.7	1.5	0.00003	4.6
Other symptoms involving abdomen + pelvis (789)	7.5	2.0	0.00003	4.1
Functional digestive disorders, NEC (564)	10.0	3.1	0.00001	3.5
Pain + other symptoms associated with female genital organs (625)	13.8	4.3	<0.00001	3.5
Anxiety, dissociative + somatoform disorders (300)	19.2	8.0	<0.00001	2.8
General symptoms (780):	16.7	7.5	0.00003	2.5
Sleep disturbances (780.5)	6.7	2.8	0.006	2.5
Other general symptoms (780.9)	10.5	2.4	<0.00001	4.8
Disorders of uterus, NEC (621)	22.6	10.5	<0.00001	2.5
Diseases of esophagus (530):	23.0	11.4	0.00001	2.3
Esophageal reflux (530.81)	21.3	11.1	0.0001	2.2
Symptoms involving head/neck (784):	11.3	5.2	0.001	2.3
Headache (784.0)	10.5	4.5	0.0007	2.5
Other disorders involving soft tissues (729):	18.4	9.1	0.00008	2.3
Myalgia + myositis, unspecified (729.1)	16.3	6.1	<0.00001	3.0
Other + unspecified disorders of back (724)	15.5	7.8	0.0005	2.2
Other postprocedural states (V45)	10.5	5.0	0.003	2.2
Adjustment reaction (309)	10.5	5.3	0.005	2.1
Depressive disorder, NEC (311)	25.1	14.4	0.0001	2.0
Nonspecific abnormal findings on radiological + other examination of body structure (793)	20.5	11.9	0.0009	1.9

We now know there is clear association between pelvic symptoms, pain from pelvic floor muscle dysfunction and other pain syndromes like fibromyalgia. Adams in 2014 reported that the prevalence of fibromyalgia in women evaluated for initial urogynecology consultation during the study period was 114 out of 1,113 (7 %). Women with fibromyalgia reported significantly higher symptom bother scores related to pelvic organ prolapse, defecatory dysfunction, urinary symptoms, and sexual function: PFDI (p =0.005), PFIQ (p=0.010), and PISQ (p=0.018). Women with fibromyalgia were found to have a higher BMI (p=0.008) and were more likely to report a history of sexual abuse, OR 3.1 (95 % CI 1.3, 7.9), and have levator myalgia on examination, OR 3.8 (95 % CI 1.5, 9.1). In a linear regression analysis, levator myalgia was found to be the significant factor associated with pelvic floor symptom bother (Adams et al, Int Urogynecol J, 2014 25:677–682.)

Karp et al reported the 1-year prevalence of migraine in women with pelvic pain to be 3 times that of the general population (53% vs 18%) (Karp BI, et al., Migraine in women with chronic pelvic pain with and without endometriosis. *Fertil Steril*. 2011;95:895-899.). Gordon subsequently states that we do not know if these disorders are related. (Gordon et al, Evaluation of the Frequency and the

Association of Sexual Pain and Chronic Headaches *Headache* 2014;54:109-115)

Patients with chronic pain syndromes have more pain after surgery

A difficult problem is that once a patient with a chronic pain syndrome has exacerbation of pain, or another surgical insult, the pain may not resolve. The reported rate at which pain is relieved with surgical removal of mesh in several reports ranges from 50–78% but little is known about risk factors for persistent pain (Skala CE, et al. Mesh complications following prolapse surgery: management and outcome. Eur J Obstet Gynecol Reprod Biol. 2011;159:453–456, Marcus-Braun N, et al., Persistent pelvic pain following transvaginal mesh surgery: a cause for mesh removal. Eur J Obstet Gynecol Reprod Biol. 2012;162:224–228, Margulies RU, et al., Complications requiring reoperation following vaginal mesh kit procedures for prolapse. Am J Obstet Gynecol. 2008;199:678, Ridgeway B, et al. Early experience with mesh excision for adverse outcomes after transvaginal mesh placement using prolapse kits. Am J Obstet Gynecol. 2008;199:703) .

Some hypothesize that patients with preexisting pain syndromes have underlying pathophysiology predisposing them to persistent pain, even after mesh has been removed. Our approach is to manage expectations by explaining that mesh removal *may be* one component of a broader treatment plan, which may also include other modalities such as neuropathic pain medications, trigger point injections and physical therapy. This reinforces that these patients need aggressive / continued management of their pelvic floor muscles, and lack of follow up and compliance to a prescribed pelvic floor program may allow persistence of symptoms.

Urgency Symptoms

As discussed, another factor driving surgeons to use tension free MUS was the observed decrease in both worsening urgency symptoms and new onset urgency

symptoms. When I was a fellow in 1992, based on synthesis of the literature and scientific meetings, I would quote women who were considering fascial vaginal sling a 1/3 rate of new, bothersome urge symptoms, and 1/3 rate of continued urgency symptoms, each of which may require more treatment. Over the next 10 years as we realized fascial bladder neck slings were too tight, we tied them more loosely. I progressed to quoting the worsening urgency rate at 1/10, but still a 1/3 rate of continuing urgency. However, the tension free MUS slings have greatly reduced these urgency symptoms. In TOMUS, we observed a 12-14% persistent urge rate for TO / RP sling and a 0 – 0.3% new urgency rate. This was a critical clinical difference again that favored these techniques over what we had been doing surgically for SUI. We have evaluated the reasons for patient dissatisfaction after sling surgery and urgency symptoms are a leading factor.

Bladder outlet obstruction

Women who cannot void well after a SUI surgery have one of two problems. She may have trouble voiding (from a weak bladder muscle, neurologic disease or some other functional voiding issue) or the SUI surgery may be too tight. This is one reason women need to have a good history, physical examination and post void residual volume before making the decision for surgery. Many clinicians also do pre operative urodynamic testing to evaluate bladder muscle function.

Using TOMUS data, we observed a 2.7% incidence of obstructed voiding after RP sling and a 0% incidence after TO sling. This is what we were observing clinically, and was similar to what others had reported. The tension free placement and mid urethral location of the MUS have combined to dramatically reduce a dreaded complication that surgeons struggled with when using fascial slings. The avoidance of bladder obstruction seems to be a large piece of the puzzle that drove surgeons to adopt both the RP and TO MUS. Reinforcing this observation was the study by Sirls et al (2013) that showed surgeon clinical decision making was most influenced by the perception of whether the patient would experience obstructed voiding after their proposed sling. Surgeons

described the most common reason to modify their treatment plan based on urodynamic data was to avoid obstruction by planning to make the sling placement looser.

Importance of Urge UI and obstructive voiding symptoms

Early postoperative voiding dysfunction or urinary retention is more common after the RP MUS than TO MUS. Early intervention to loosen or cut the sling is may be considered when women cannot void or have significant obstructive symptoms as early as 3-4 days. Several authors have reported 12-month success after early sling loosening at postop day 3–10. Women with persistent obstructed voiding despite tape loosening may require formal sling lysis or urethrolysis might be to prevent long-term voiding dysfunction.

Kenton 2015 presented 5 year follow up on TOMUS patients (Kenton, 2015). She reported that though at 5 years there was a 7.5% greater success in the RP MUS arm vs. the TO arm, urinary symptoms and QoL worsened with time with women with a RP sling reporting greater urinary urgency ($p< 0.001$), more negative impact on QoL ($p = 0.02$) and worse sexual function ($p= 0.001$). Though treatment success rates were slightly higher after RP sling, a greater proportion of women who had TO sling reported their urinary status was very much or much better. This perception of greater overall improvement despite more SUI symptoms may be explained by higher rates of urgency urinary incontinence and irritative symptoms in women after RP sling that essentially equalized the slight advantage of the RP sling over TO sling with respect to treatment success. In general, urinary symptoms and QOL measures showed greater overall improvement after TO sling, suggesting that the trend toward factoring better treatment success in the RP group may come at the cost to quality of life and other symptoms. These findings are similar to what was observed in the Sister trial (Albo 2007) where fascial sling rates had slightly

higher 5 year continence rates than the Burch but similar to the TOMUS study, satisfaction trends over time did not differ significantly between groups. They reported that the urgency and urge incontinence that the fascial sling patients experienced impacted their subjective sense of improvement and overall satisfaction. More urge and urge incontinence may be the trade off in the longer term for higher treatment success with SUI surgery.

The 2015 Cochrane review reported that the rates of postoperative voiding dysfunction (POVD) was assessed in 37 trials with 6200 patients. This showed significantly lower rates in the TO group than in the RP group (RR 0.53 95% CI 0.43 to 0.65; Analysis 1.17). The average POVD rate across both groups was 5.53% and, using this as the assumed control rate in the RP group, there were 26 fewer POVD per 1000 in the TO group (95% CI from 19 to 32 per 1000 fewer). This review did not show a difference in the rate of urge and urge incontinence between RP and TO sling groups. The 31 trials (4923 women) that reported de novo urgency and urgency urinary incontinence (UUI) showed no statistically significant difference between the two groups (RR 0.98, 95% CI 0.82 to 1.17; Analysis 1.18). In the short term the average rate of de novo urgency/UUI across both groups was 8.35% and, using this as the assumed control rate in the RPR group, there were two fewer cases per 1000 in the TOR group (95% CI from 15 per 1000 fewer to 14 per 1000 more). Equally, in themedium termthe rate of de novo urgency and UUI was not significantly different (RR 0.98, 95% CI 0.55 to 1.73, Analysis 1.19). Laurikainen 2007 reported long-term data for de novo urgency and UUI for 253 women; this showed no difference between the groups (RR 0.81, 95% CI 0.18 to 3.53; 253 women; Analysis 1.20). Four trials with 853 women withDO showed a rate of 8%in both groups (RR 1.00, 95% CI 0.58 to 1.73; Analysis 1.21). In one trial of women with MUI (Laurikainen 2007), 84% who had pre-existingmoderate or severe urinary frequency and urgency symptoms were cured of these symptoms post operatively at the five-year follow-up.

Sexual Function

Sexual function was evaluated as early as 1998 by Maaita et al, published in 2002. (*BJU International* (2002), 90, 540–543) who concluded that "there was no significant change in sexual function or activity after the TVT procedure and patients can thus be reassured that this operation will not affect their sex life". More recent prospective study comparing the effect of the tension-free vaginal tape (TVT) to the Monarc sling on sexual function in women with urodynamic stress incontinence (USI) and intrinsic sphincter deficiency (ISD) (De Souza, et al, Int Urogynecol J. 2012 Feb;23(2):153-8. doi: 10.1007/s00192-011-1461-9. Epub 2011 Jul 21.) Eighty-seven sexually active women with USI and ISD were enrolled. Sexual function was assessed pre-operatively and at 6 and 12 months post-operatively by history, PISQ-12, UDI-6 and IIQ-7 questionnaires. A significant increase was detected in PISQ-12 score following both TVT and Monarc insertion. This score was greater in the TVT group at 6 months but not at 12 months when compared to the Monarc group. A significant decrease in UDI-6 and IIQ-7 score was detected. Specifically, coital incontinence and fear of leakage were reduced in both groups, and no change in dyspareunia or orgasm intensity was found.

Zyczynski et al reported on sexual activity 2 years after MUS in TOMUS trial participants (Am J Obstet Gynecol 2012;207:421.e1-6.) Significant, similar improvements in sexual function were seen in both midurethral sling groups. Mean Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire scores increased from 32.8 at baseline to 37.6 at 6 months and 37.3 at 24 months ($P<0.0001$). Dyspareunia, incontinence during sex, and fear of incontinence during sex each significantly improved after surgery. Preoperative urge incontinence was associated with abstinence after surgery ($P=.02$); postoperative urge incontinence negatively impacted sexual function ($P=.047$). The proportion of women who were sexually active after surgery was 67.2% at 6 months and 64.1% at 24 months. The proportion of sexually active women did not differ significantly from baseline ($P=.69$) and was not associated significantly with

treatment assignment (*P*=.58), failure status (*P* =.26), concomitant surgery (*P* = .19), or baseline stage of prolapse (*P*=06). Neither intra- nor postoperative complications were associated significantly with sexual activity or function. Pain with intercourse was reported by 153 of 406 of sexually active women (38%) at baseline and decreased to 27% at 12 months after surgery (*P*=.003). Self-reported UI and the fear that incontinence might occur during sexual activity also significantly improved by 12 months after surgery, regardless of sling route (*P* <0 .0001 for both). The important conclusions are that among sexually active women who had an MUS (retropubic or transobturator) placed, sexual function as reported on the PISQ-12 improved significantly over
the first 2 years after surgery without notable differences between the 2 studied techniques. Notably, they did not detect any decrease in the proportion of women who reported sexual activity during these 2 years, and sexually active women reported less dyspareunia.

These findings are consistent with those of other surgical treatment trials for SUI. Participants in the Stress Incontinence Surgical Treatment Efficacy (SISTEr) trial, which compared the fascial sling and Burch urethropexy, also reported improvements in sexual function, with a statistically and clinically significant reduction in the proportion of women who experienced pain during sexual activity.

Schimpf reported that though their meta-analysis shows dyspareunia is rare with any type of sling, it is somewhat more common with a minisling (0.99%) than either a retropubic (<0.001%) or obturator (0.16%) sling (Schimpf, 2014).

Quality of Life after mesh MUS

All of these condition specific measures have been used to evaluate quality of life.

- Incontinence Impact Questionnaire (IIQ-7).
- Urogenital Distress Inventory (UDI-6).
- International Consultation on Incontinence Questionnaire (ICIQ).
- Urinary Incontinence Quality of Life Scale (I-QOL).

- Kings Health Questionnaire (KHQ).
- Bristol Female Lower Urinary Tract Symptoms questionnaire (BFLUTS).
- Women Irritative Prostate Symptoms Score (W-IPSS).
- Urinary Incontinence Severity Score (UISS).
- Detrusor Instability Score (DIS).
- A Visual Analogue Scale (VAS).
- CONTILIFE.

These general measures have been used to evaluate general quality of life outcomes.

- EuroQoL 5-Dimensional Classification Component Scores (EuroQoL-5D).
- Short-Form Health-Related QoL (SF-36).
- Patient Global Impression of Severity (PGI-S).
- Patient Global Impression of Improvement (PGI-I).

The 2015 Cochrane review reports that in general, with the exception of Araco 2008, all trials found that women's QoL improved significantly after both RP and TO sling, but no statistically significant differences were found between the randomized groups. Only the Araco 2008 trial found the I-QOL scores to be statistically significantly higher postoperatively after the retropubic approach.

A UITN study on TOMUS women randomized to RP or TO MUS showed that condition-specific QoL improves after midurethral sling surgery, regardless of approach (RP or TO) or QoL measure. It should be reassuring to surgeons and patients alike that, after midurethral sling surgery for SUI, patients report about 80% improvement in QoL that is sustained at least 2 years. Women with the greatest QoL improvement were younger, reported more improvement in UI symptom bother and had "successful surgery." These data should be integral in counseling women prior to midurethral sling surgery for SUI (Sirls 2012).

Interestingly, in the study on predictors of improved QOL after surgery for SUI in the SISTEr (Burch vs. fascial pubovaginal sling) they identified decreased UI bother, improved severity, and younger age, as well as Hispanic ethnicity and assigned treatment i.e, having had a Burch surgery. Why did patients who had a Burch surgery have improved QOL when the sling surgery clearly cured SUI better? Because the Burch was less obstructive than the sling, patients had less obstructed voiding, less urgency, and ended up more satisfied. This is the same effect I have seen for more than 10 years after mesh MUS surgery. I have never before seen so many satisfied women, happy with their outcome. A study looking at patient satisfaction showed that one year after surgery, both TVT and TOT treatment groups demonstrated a high level of satisfaction with respect to urine leakage (retropubic 85.9% compared with transobturator 90.0%; P=.52), urgency to urinate, frequency of urination, capability of physical activity, social activity, ability to engage in sexual activity, and from an emotional standpoint (Wai, C. Obstet Gynecol 2013). They concluded "The high level of satisfaction seen after midurethral sling procedures is associated with greater objective and patient-perceived improvement of stress incontinence and fewer complications."

Position Statements

The favorable efficacy to safety profile of the MUS like TVT and TVT-O have led to their recognition as a first line surgical option, the gold standard, and the standard of care for the surgical treatment of SUI.

There are several professional society guidelines and position statements that recognize the suitability and use of MUS like TVT and TVT-O in treating SUI. The AUA's 2011 Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of SUI states

Suburethral synthetic polypropylene mesh sling placement is the most common surgery currently performed for SUI. Extensive data exist to support the use of

synthetic polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative surgeries.

Advantages include shorter operative time/anesthesic need, reduced surgical pain, reduced hospitalization, and reduced voiding dysfunction. Mesh-related complications can occur following polypropylene sling placement, but the rate of these complications is acceptably low. Furthermore, it is important to recognize that many sling-related complications are not unique to mesh surgeries and are known to occur with non-mesh sling operations as well.

The 2013 NICE (National Institute for Health and Care Excellence) Clinical Guideline 171 Urinary incontinence: The management of urinary incontinence in women observes that "When offering a synthetic mid-urethral tape procedure, surgeons should: Use procedures and devices for which there is currently high quality evidence of efficacy and safety". It further provides that "The guideline only recommends the use of tapes with proven efficacy based on robust RCT evidence…. At the time of publication (September 2013) the following met the Guideline Development Group criteria: TVT or Advantage for a 'bottom-up' retropubic approach; TVT-O for an 'inside-out' transobturator approach…"

The September 2012 EAU (European Association of Urology) Guidelines on Surgical Treatment of Urinary Incontinence also concludes "There has been a rapid adoption of midurethral synthetic sling insertion as the first-line surgical option for SUI because it is effective, it is less invasive, and patients recover more quickly." Similar conclusions have been reached by ICS, which in its July 2013 Fact Sheet: A Background to Urinary and Faecal Incontinence it is observed that "Worldwide, midurethral slings compromised of synthetic mesh have become the treatment of choice for SUI. Long-term data are robust and demonstrate durable efficacy with a very low complication rate, particularly in experienced hands."

The AUGS / SUFU position statement on MUS for SUI (2014) includes the following

"We are concerned that the multimedia attention has resulted in confusion, fear, and an unbalanced negative perception regarding the midurethral sling as a treatment for SUI. This negative perception of the MUS is not shared by the medical community and the overwhelming majority of women who have been satisfied with their MUS. Furthermore, the FDA website states that: "The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year."[5]."

They argue that

1. Polypropylene material is safe and effective as a surgical implant.

Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh). As an isolated thread, polypropylene is a widely used and durable suture material employed in a broad range of sizes and applications. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. [6, 7] As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years [8].

2. The monofilament polypropylene mesh MUS is the most extensively studied anti-incontinence procedure in history.

A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of the MUS as a treatment for SUI [9]. There are greater than 2000 publications in the scientific literature describing the

MUS in the treatment of SUI. These studies include the highest level of scientific evidence in the peer reviewed scientific literature [9]. The MUS has been studied in virtually all types of patients, with and without comorbidities, and all types of SUI. Multiple randomized, controlled trials comparing types of MUS procedures, as well as comparing the MUS to other established non-mesh SUI procedures, have consistently demonstrated its clinical effectiveness [9-12] and patient satisfaction [12]. Among historical SUI procedures, the MUS has been studied as long in follow-up after implantation as any other procedure and has demonstrated superior safety and efficacy [8]. No other surgical treatment for SUI before or since has been subject to such extensive investigation.

3. Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for our patients.

Since the publication of numerous level one randomized comparative trials, the MUS has become the most common surgical procedure for the treatment of SUI in the US and the developed world. This procedure has essentially replaced open and transvaginal suspension surgeries for uncomplicated SUI. There have been over 100 surgical procedures developed for the management of SUI and there is now adequate evidence that the MUS is associated with less pain, shorter hospitalization, faster return to usual activities, and reduced costs as compared to historic options that have been used to treat SUI over the past century. Full-length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard for stress incontinence surgery [13]. Over 3 million MUS have been placed worldwide and a recent survey indicates that these procedures are used by > 99% of AUGS members [14].

4. The FDA has clearly stated that the polypropylene MUS is safe and effective in the treatment of SUI.

The midurethral sling was not the subject of the 2011 FDA Safety Communication, "Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Vaginal Placement for Pelvic Organ Prolapse."[3]. In this document, it was explicitly stated: "The FDA continues to evaluate the effects of using surgical mesh for the treatment of SUI and will report about that usage at a later date." In 2013, the FDA website stated clearly that: "The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year." [5].

AUGS and SUFU conclude

"This procedure is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our organizations which are dedicated to improving the lives of women with urinary incontinence."

The 2013 ICS urinary incontinence factsheet states

"Definitive therapy for SUI is surgical and involves restoring urethral support through use of a sling. Worldwide, midurethral slings comprised of synthetic mesh have become the treatment of choice for SUI. Long-term data are robust and demonstrate durable effi cacy with a very low complication rate, particularly in experienced hands. Various techniques for sling placement and diff erent meshes are employed according to physician preference, but all appear to be equally eff ective. An additional benefi t of the slings is that they are easily combined with procedures for the repair of POP".

The 2014 AUGS / SUFU FAQ by patients on MUI for SUI states

"The mid-urethral sling procedure is the most studied surgery to treat stress urinary incontinence and there have been over 2,000 articles published about it. Results of these studies have appeared in prestigious medical journals such as the New England Journal of Medicine. Two large government funded studies have evaluated the mid-urethral sling's safety and efficacy – both found the

procedure to have a low complication rate and a high success rate. Other large scientific studies from around the world have supported the safety and efficacy of the mid-urethral sling."

The April 2013 FDA position statement stated

"The most common complications reported through MDRs for surgical mesh slings for SUI repair, in descending order of frequency, include: pain, mesh erosion through the vagina (also called exposure, extrusion or protrusion), infection, urinary problems, recurrent incontinence, pain during sexual intercourse (dyspareunia), bleeding, organ perforation, neuro-muscular problems and vaginal scarring. Many of these complications require additional medical intervention, and sometimes require surgical treatment and/or hospitalization. ***With the exception of mesh erosion, the above complications can occur following a non-mesh surgical repair for SUI****."*

Schimpf's 2014 meta analysis reported Society for Gynecologic Surgeons Systematic Review Group created a ***"Sling surgery for Stress Urinary Incontinence in Women Clinical Practice Guidelines"*** *and recommend the following.*

Midurethral sling vs. Burch (open or laparoscopic)

For women considering midurethral slings or Burch procedures for treatment of SUI, we suggest either intervention for objective and subjective cure and that the decision be based on 1) which adverse events are of greatest concern to the patient and 2) any other planned concomitant surgeries (vaginal vs. abdominal route). (1A)

- Midurethral slings may result in lower rates of perioperative adverse events such as blood loss, postoperative pain, OR time, hospital stay, bowel injury, wound infection, and hematomas. (1C)
- Burch procedures may result in lower rates of return to the OR for retention, erosion, overactive bladder symptoms, and groin pain. (1C)

Pubovaginal sling (biologic and synthetic) vs. midurethral sling (only TVT was studied)

For women considering a pubovaginal or midurethral sling for treatment of SUI, we recommend a midurethral sling for better subjective cure outcomes. (2C)

- Midurethral slings may result in lower rates of perioperative outcomes such as OR time, blood loss, and hospital stay. (2D)
- Pubovaginal slings may result in lower rates of adverse events such as urinary tract infection and vaginal perforation. (2D)

My opinion reflects the AUA's opinion that any restriction on the use of synthetic polypropylene mesh suburethral slings would be a disservice to women who choose surgical correction of SUI.

Type 1 mesh and cancer

Despite long-term studies supporting the efficacy and safety of macroporous, monofilament polypropylene mesh for the treatment of stress urinary incontinence, there have been concerns regarding the general risks of using mesh in transvaginal surgery. Concerns have been raised recently about synthetic midurethral slings and a possible link with malignancy (Ostergard DR, Azadi A. To mesh or not to mesh with poly- propylene: does carcinogenesis in animals matter? Int Urogynecol J. 2014;25:569-571). These concerns are based on rodent models that demonstrated a high rate of sarcoma formation after subcutaneous implantation of polypropylene. However, further investigation suggests that the risk of malignancy may be related to the surface area and morphology of the implanted material more than to the composition of the material. Perforated materials have been shown to have a lower risk of malignancy (McGregor DB, et al. Evaluation of the carcinogenic risks to humans associated with surgical implants and other foreign bodies - a report of an IARC Monographs Programme Meeting. International Agency for Research on Cancer. Eur J Cancer. 2000;36:307-313.)

King et al reported on all sling procedures performed at their institution from 2004 to 2013, 2545 procedures were performed. Of these, 2361 (96.3%) underwent poly- propylene midurethral sling placement. Average follow-up after sling placement was 42.0 ± 38.6 months, with follow-up extending up to 122.3 months. The rate of bladder cancer after the sling procedure was 1 of 2361 (0.0%), with the same rate of vaginal cancer. No sarcomas were noted. Overall, the rate of malignancy after polypropylene mesh midurethral sling placement in their series was 0.0% (2 of 2361). With a mean follow-up of almost 4 years and follow-up extending up to a maximum of 122.3 months, their series does not support any association between the polypropylene mesh used for midurethral slings and the development of malignancy in humans (King et al, UROL 84: 789-792, 2014).

Moalli argues that "..publications derived from a skewed interpretation of the literature and not solid evidence based on scientific data can lead to baseless damaging media hype and unscrupulous jury awards. It would be a tragedy for women worldwide if non-scientifically based articles regarding the potential hazards of polypropylene incited a spiraling course for the best (highest success rate and minimal morbidity) surgical procedure developed to date.." She states " As treating physicians, we must let science and clinical studies determine our practice. More importantly, we must align with the millions of women who have been successfully treated with mesh with absolutely no evidence of systemic complications (including cancer) and who have regained control of their quality of life." (Moalli et al, Polypropylene mesh: evidence for lack of carcinogenicity. Int Urogynecol J. 2014 May;25(5):573-6.).

My Training and Experience with Midureteral Sling Training

Though I was an experienced vaginal reconstructive surgeon who had already been doing sling and abdominal bladder suspension procedures for more than 10 years, I needed additional training before using the doing a TVT or TOT procedure. I attended a cadaver laboratory, and had both lecture and hands on

experience with the TVT and then TOT. I then visited Aaron Kirkemo in Minnesota and observed him do several live surgeries. There were several technical differences we discussed and I observed during these training sessions. I have been a proctor for numerous cadaver laboratories with different sling companies over the last 10 years. In addition, I have performed live retropubic and transobturator sling surgeries for other surgeons after they completed their cadaver laboratory training. These surgeons were experienced vaginal surgeons that had not yet used the TVT or TOT, and they wanted to watch a real surgery. When I was training, the Ethicon staff were attentive and helpful with getting my questions answered by the expert surgeon teaching the course. The cadaver laboratory was thorough in providing hands on experience with the trocar and it's use. I felt confident after the laboratory and after observing several live surgeries felt I was ready to use TVT and TOT.

When I proctored cadaver laboratories, Ethicon staff were focused on evaluating the surgeons skills I was teaching and observing. They would ask me if I thought this person had sufficient understanding and demonstrated competence with the device, and whether I thought they were capable to safely and effectively use the device.

The Packaged Kits and Printed Information

I have the TVT and TOT AUA Patient Handout in our office and give them to patients. I also discuss the FDA Public Health Notices from both 2008 and 2011. I feel a critical, mandatory preoperative step is a comprehensive consultation with each patient. The surgeons consultation, explaining the benefits, risks and potential complications of the surgical options in detail, is the corner stone of the surgeon patient relationship and of surgical decision making.

Similarly, in my opinion the product information form, provided with the TVT and TOT systems, should not be considered the definitive, comprehensive document on the risks and complications of either procedure. I believe there is no written

document that can serve as a single, comprehensive source of all information about the risks of any surgical procedure. Instead, the surgeon must discuss all relevant risks and complications of any potential or planned surgery in clear language the patient can understand. This includes all surgery related issues as well as other relevant issues include risks of allergy, anesthesia, blood clots, pulmonary embolism and even death. The TVT and TOT product information form conveyed the pertinent potential benefits and risks associated with the procedure, many of which are common to other mesh sling procedures including the risks of mesh exposure. I find it important that the TVT-O IFU includes the following.

Important:

This package insert is designed to provide instructions for use of the GYNECARE TVT™ Obturator System, including the GYNECARE TVT Obturator device, Helical Passers and Atraumatic Winged Guide. It is not a comprehensive reference to surgical technique for correcting SUI (Stress Urinary Incontinence). The device should be used only by physicians trained in the surgical treatment of stress urinary incontinence and specifically in implanting the GYNECARE TVT Obturator device. These instructions are intended for general use of the device. Variations in use may occur in specific procedures due to individual technique and patient anatomy.

WARNINGS AND PRECAUTIONS

- Users should be familiar with surgical technique for urethral suspensions and should be adequately trained in the GYNECARE TVT Obturator procedure before employing the GYNECARE TVT Obturator device.
- As with other incontinence procedures, de novo detrusor instability may occur following a sub-urethral sling procedure utilizing the GYNECARE TVT Obturator System. To minimize this risk, make sure to place the tape as described above.

ADVERSE REACTIONS

- Over correction, i.e. too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction.

It is important to recognize that surgeons obtain information from numerous sources besides the product information, including their education and training, attending conferences such as those that I have attended and presented at, the medical literature, discussion with colleagues, and their clinical experience.

Summary

It is my opinion that the mesh midurethral sling (MUS) procedures represent the most significant advances in the surgical management of female SUI that I have ever observed. My opinion is based on 25 years of clinical experience; more than 10 years performing fascial pubovaginal slings and Burch suspensions, followed by more than 10 years of placing both retropubic and transobturator mesh MUS. This opinion is formed from surgical experience and outcomes with thousands of women, reading and reviewing the literature, participating in scientific research and attending scientific meetings. I am confident that polypropylene material is safe and effective as a surgical implant.

Many randomized, controlled trials comparing types of MUS procedures, as well as comparing the MUS to other established non-mesh SUI procedures, have consistently demonstrated efficacy. MUS have been extensively studied in long term follow-up after implantation and has demonstrated superior safety and efficacy. MUS procedures have been subject to more extensive investigation than any other surgical treatment for SUI. The FDA has clearly stated that the polypropylene MUS is safe and effective in the treatment of SUI. I feel that polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for my friends, family and patients.

My rates are $750/hour for review and depositions and $1500/hour for Court testimony.

I reserve the right to supplement my opinions should new or additional information become available. I plan to review the testimony of Plaintiffs' experts and reserve the right to respond to their testimony.

Larry T. Sirls
Larry Sirls, M.D.
June 3, 2016